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HÆMOLYTIC ANÆMIA.[1]

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THE diagnosis of hæmolytic anæmia may be a simple matter requiring only clinical observation and routine laboratory investigations, or it may be elusive and depend on red-cell survival studies and the most elaborate techniques of immunology and biochemistry. It is the object of this paper to discuss the significance of observations usually available to the clinician in the diagnosis of the more difficult case of hæmolysis.

The pathogenesis of hæmolytic anæmia has been greatly clarified in recent years by two advances in its study. The first is concerned with the normal rate of hæmolysis, each cell being destroyed after a life span of about 120 days. Pathological hæmolysis is therefore present when the life span of the cell is something less than 120 days, and this is the one essential criterion for its diagnosis. The second concept is that the destruction of the cell, whether premature or not, may be due to an intrinsic defect or an extraneous agent.

[1] Based on a paper read at a seminar on hæmatology at the Red Cross Blood Transfusion Service, Sydney, on July 18, 1957.

MECHANISMS OF HÆMOLYSIS.

The physiological death of the red cell has been considered to be the result of disintegration and phagocytosis; the disintegration is the result of the continual buffeting and wear and tear occurring during its lifetime—something akin to the wearing thin and bursting at the seat of a worn pair of pants. This is obviously naïve, and a much more attractive hypothesis is concerned with the efficiency of enzyme processes within the cell. A defect developing in these may form the basis of physiological cellular disintegration, as well as the pathological destruction of intrinsic defect hæmolysis.

An example with some evidence to support it concerns the formation of choleglobin within the cell. The oxidation of hæmoglobin to methæmoglobin is hastened by the presence of hydrogen donors (ascorbic acid or reduced glutathione normally present in the cell) by formation of the intermediary hæmoglobin peroxide. If the donors are present in excess, some of the peroxide is converted to another pigment, choleglobin. This may reach a concentration of 20% in the cell, giving a dusky or green coloration. Its presence leads to increased fragility and easy phagocytosis. An enzyme, catalase, prevents the formation of hæmoglobin peroxide, and may be a factor in prolonging the life of the red cell. It may be significant that human erythrocytes (life span 120 days) are rich in

catalase, while avian cells (life span 28 days—Hevesy and Ottesen, 1945) contain little (Foulkes and Lemberg, 1949).

As well as intrinsic mechanisms leading to cell destruction, hæmolytic agents can be extracted from normal plasma and are present in normal tissues (Ponder, 1951). These include lipoproteins, soaps and bile salts. After a fatty meal, the concentration of soaps in a dog's plasma rises from 1·0 to 6·0 milligrammes per 100 millilitres, enough to increase the rate or red-cell destruction by one-third. The anæmia due to moth-ball (naphthalein) intoxication is due to potentiation of the soap and fatty acid lysins normally present in plasma; naphthalein is not in itself hæmolytic. Phenothiazine, an anthelminthic used for animals, may also produce hæmolytic anæmia by potentiating the lytic effect of lysolecithin.

The relative importance of the intrinsic and extrinsic factors in physiological red-cell destruction is a matter of speculation, and the problem is further complicated by the presence of anti-lytic substances, of which cholesterol may be an example.

Pathological hæmolytic processes also fall into two groups. The first, including the familial hæmolytic anæmias (congenital spherocytosis and congenital non-spherocytic anæmias), sickle-cell anæmia and other anæmias associated with the abnormal hæmoglobins, are due to an intrinsic defect, such that the cells have a shortened life whether in the circulation of the patient or transfused into a normal subject.

Red-cell metabolism is predominantly glycolytic, and in the absence of glycolysis, cation transport and lipid synthesis in the membrane fail, and swelling and other morphological changes develop in the cell. These processes can be demonstrated by observing glucose uptake from and radioactive phosphorus exchanges with the suspending solution. In some types of congenital non-spherocytic anæmia, a fault in glucose uptake by the cells can be demonstrated; and in these, together with congenital spherocytic anæmia and the hæmolytic anæmia sometimes associated with the administration of "Primaquine", abnormalities in phosphate exchange have been observed. These metabolic defects are not present in other intrinsic hæmolytic processes, such as thalassæmia and the hæmoglobinopathies (Prankerd, 1957).

In the second group the cells are normal and survive normally if transfused into a normal subject. An extrinsic agent is present in the plasma, and destroys prematurely the patients' own cells and also cells transfused from a normal subject. This latter group includes the immune types of hæmolytic anæmias, in which the damage occurs at the cell surface and may involve the action of complement (Reader, 1955), and certain inorganic, organic and bacterial toxins.

The separation of these two types of hæmolytic process has been made possible by the techniques of red-cell survival study introduced by Ashby in 1919 and, more recently, by methods using red cells tagged with radioactive chromium (Nechelles *et alii*, 1953).

THE DIAGNOSIS OF HÆMOLYSIS.

The investigation of a patient with hæmolytic anæmia proceeds in two steps: first, the demonstration that the anæmia is in fact hæmolytic—that the red-cell life is shortened; and second, the determination of the mechanism of hæmolysis. There may be confusion, however, in the case in which pathological hæmolysis is occurring, but the patient is not anæmic. This situation will be discussed in detail later.

A second complicated group comprises the so-called hæmopathic hæmolytic anæmias, in which hæmolysis is secondary to an underlying disease, cure of which, if possible, automatically corrects the hæmolytic process. This has been demonstrated in rheumatoid arthritis, nephritis, hepatic disease, leukæmia, and also pernicious anæmia and iron-deficiency anæmia. The hæmolysis may be due to intrinsic or extrinsic defect, and some of the survival studies are summarized in Table I.

In some of these hæmopathic anæmias, the anæmia may be of such severity as to represent for a time the major therapeutic problem, and may require transfusion, corticosteroids and even splenectomy. Frequently such patients present with the anæmia, and the primary disease may be overlooked unless it is specially sought. This secondary hæmolytic anæmia may be associated with autoantibodies giving a positive direct Coombs reaction. Hodgkin's disease, lymphatic leukæmia, diffuse lupus erythematosus and rheumatoid arthritis have been associated with a hæmolytic anæmia of this type.

TABLE I.

Red-Cell Survival Studies Demonstrating Hæmopathic Hæmolysis.

Donor's Condition.	Recipient's Condition.	Number Studied.	Survival (Days): Average of Group.	Author.
Normal	Rheumatoid arthritis.	18	84	Alexander *et alii* (1956).
Acute nephritis	Normal.	1	36	Chaplin and Mollison (1953).
Progressive nephritis.	Normal.	3	36	Chaplin and Mollison (1953).
Liver failure ..	Normal.	5	40	Chaplin and Mollison (1953).
Pernicious anæmia	Normal.	2	52	Singer *et alii* (1948).
Pernicious anæmia (remission).	Normal.	1	120	Singer *et alii* (1948).
Chronic myeloid leukæmia.[1]	Normal.	2	74	Berlin *et alii* (1951).

[1] Patient's own cells labelled with C^{14}

The Clinician's Approach to Diagnosis.

While the difficult case of hæmolytic anæmia may require highly specialized techniques, critical information may be obtained from routine laboratory studies of the hæmoglobin level, reticulocyte count and pigment changes. These may in themselves be diagnostic of pathological hæmolysis; but the results are sometimes misleading, and the clinician must be prepared to interpret apparently anomalous findings.

The Anæmia.

A fall in circulating hæmoglobin, reflected by a fall in hæmoglobin concentration, may result from hæmorrhage, pathological hæmolysis or inadequate marrow synthesis. Some physiological parameters for a subject weighing 70 kilograms are shown in the following tabulation:

Some Hæmatological Parameters for a Normal Subject.

Body weight: 70 kilograms.

Blood volume (75 millilitres per kilogram): 5050 millilitres.

Plasma volume: 2750 millilitres.

Red-cell mass: 2250 millilitres.

Hæmoglobin mass (15 grammes per 100 millilitres): 750 grammes.

Red-cell life span: 100 to 120 days.

Daily turnover:

- Red cells: 22·5 millilitres (50,000 per cubic millimetre).
- Hæmoglobin: 7·5 grammes (0·15 gramme per 100 millilitres).
- Bilirubin (urobilinogen): 262 milligrammes.[1]

Reticulocyte count (1% of red-cell count = daily output of red cells): 50,000 per cubic millimetre.

With red-cell wastage at the normal physiological rate, approximately 1% of the hæmoglobin mass is lost daily. Thus, with complete failure of marrow replacement, the fall in hæmoglobin mass will be 7·5 grammes per day, and, provided that the blood volume remains unchanged,

[1] Breakdown of one gramme of hæmoglobin gives rise to 35 milligrammes of bilirubin.

the fall in concentration will be 0·15 gramme per 100 millilitres per day. However, there is usually an increase in plasma volume with anæmia, and the fall in concentration may be greater. Whyte (1956) showed an average increase in blood volume of 250 millilitres in 12 of 14 patients with anæmia, but in some individuals it was as much as 20% of the total plasma volume. In such a case, even if the anæmia is due to marrow aplasia, one could expect a rate of fall of hæmoglobin concentration of something greater than 0·15 gramme per 100 millilitres per day. To take an example, the maximum fall in hæmoglobin concentration over a week due to marrow aplasia alone would be 1·0 gramme per 100 millilitres. If during this week the blood volume increased by 20%, the fall in concentration would be from (say) 7·0 grammes per 100 millilitres to 6·0 grammes per 120 millilitres—that is, to 5·0 grammes per 100 millilitres. Thus a fall in hæmoglobin concentration of two grammes in a week may, under exceptional circumstances, be due to marrow aplasia alone; but falls of more than this, or repeated falls of more than one gramme per week, must be diagnostic of pathological hæmolysis, provided hæmorrhage can be excluded.

It should be noted that conclusions from the rate of fall of hæmoglobin level should not be drawn except on a series of observations, because of the usual errors of hæmoglobin determination. Figure I shows hæmoglobin values in two cases, in which the nature of the anæmia was obscure, but the several episodes of rapid fall left no doubt that hæmolysis played a major part.

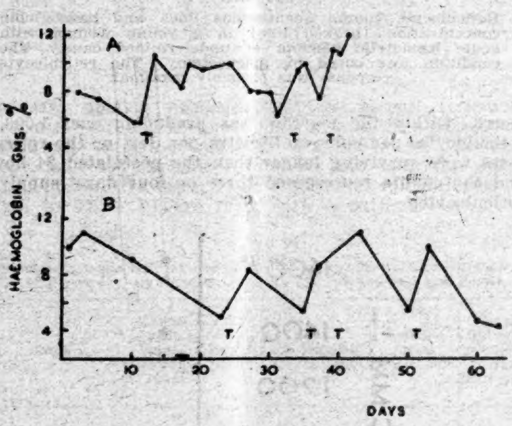

FIGURE I.

Hæmoglobin levels in two anæmic patients, in whom the cause of the anæmia was obscure. In A., suffering from pancytopenia which was later cured by splenectomy, reticulocytes were never increased, and the serum bilirubin level was repeatedly less than 0·5 milligramme per 100 millilitres. In patient B., reticulocytosis and jaundice were noted subsequently, but were inconstant. No evidence of hæmorrhage could be found in either patient, and because of the rapid and repeated falls in hæmoglobin concentration hæmolysis was confidently diagnosed.) (T, tranfusion.)

While a study of the rate of fall of hæmoglobin level may thus be helpful, on other occasions it may be misleading. Thus the shortened life span may be slight and the rate of fall imperceptible; or more significantly, the hæmoglobin level may be steady and normal, and yet the patient may be suffering from a hæmolytic disease in which there is considerably shortened life span of the cells. Table II shows data of two such patients.

Crosby and Akeroyd (1952) give more detailed data (Table III) of two such patients, from which they were able to demonstrate the considerable regenerative response of normal marrow. Theoretically, the physiological replacement is at the rate of 7·5 grammes of hæmoglobin per day (see tabulation on page 282) In their two patients under maximal stimulus it was 40 and 45 grammes per day—in other words, an increase of some sevenfold. It is thus apparent that healthy marrow may compensate for a shortened red-cell life span to 11 or 12 days. Hedenstedt (1947) found a normal hæmoglobin level in spite of a life span of the cells of 30 to 40 days, and Mollison (1947) and Dacie and Mollison (1943—and see Crosby and Akeroyd, 1952) 27 and 25 days respectively.

TABLE IIA.[1]

Date.	Hæmoglobin Value. (Grammes per 100 Ml.)	Reticulocytes per C. mm.	Bilirubin. (Mgm. per 100 Ml.)	Reaction to Coombs Test.	Cortisone. (Mgm. per Day.)
1955:					
May 26 ..	4·5	30,000	1·4	+	50
July 19 ..	14·1	50,000	1·4	+	50
July 27 ..	12·4	20,000			50
August 10 ..	12·0				50
August 22 ..	12·0	20,000			50
September 16	12·4				50
October 11	10·0				50
October 21 ..	10·5	70,000	1·2		25
November 15	12·0				Nil
December 5..	13·1				
1956:					
January 6 ..	13·6				
April 20 ..	12·5	82,000	0·5	+	
July 31 ..	14·1				
1957:					
January 16	13·8	55,000		+	
May 7 ..	16·5			+	

[1] A male patient, aged 68 years, with acquired hæmolytic anæmia. He was admitted to hospital and investigated between May 26, 1955, and July 21, 1955, and subsequently observed as an out-patient. He maintains a normal hæmoglobin level in spite of evidence of persisting hæmolysis.

Reticulocytosis.

Normally about 1% of circulating red cells are in the form of reticulocytes—that is, there are some 50,000 reticulocytes per cubic millimetre of blood. In considering the reticulocyte count as a measure of marrow response, it is just as well to think in terms of concentration of reticulocytes rather than of reticulocytes as a proportion of the total red cells. Thus the normal figure of 50,000 per cubic millimetre is 1% of 5,000,000 red cells, but 2% of 2,500,000 and 5% of 1,000,000.

TABLE IIB.[1]

Date.	Hæmoglobin Value. (Grammes per 100 Ml.)	Reticulocytes per C.mm.	Serum Bilirubin Content. (Mgm. per 100 Ml.)
April 1, 1956	11·5	—	1·0
June 7, 1956	11·0	100,000	—
November 9, 1956 ..	11·7	277,000	—
February 1, 1957 ..	11·0	183,000	—
September 17, 1957 ..	11·9	120,000	1·0
October 3, 1957 ..	11·5	266,000	2·2
October 8, 1957 ..	12·1	20,000	—
October 15, 1957 ..	11·3	270,000	0·8
October 22, 1957 ..	11·0	220,000	1·0

[1] This patient suffers from chronic hæmolytic anæmia with spherocytosis and increased fragility. The Coombs test has repeatedly given negative results.

Minot *et alii* (1928) have observed the alterations in the reticulocyte count in response to adequate liver therapy in 89 patients with pernicious anæmia, and their results have been widely quoted. Thus the two left-hand columns of Table IV, taken from Whitby and Britton (1957), are attributed to those authors. The figures imply a striking inverse relationship between the peak reticulocyte count and the initial red-cell count. In the third line I have calculated the reticulocyte concentration from the same data, and the picture is quite different. The fallacy of considering the proportion of reticulocytes was pointed out by Minot *et alii* in their paper.

If the normal wastage and replacement of red cells is approximately 1% of the total per day, and the proportion

of reticulocytes to total cells is 1%, it seems that the absolute reticulocyte count is a fair measure of the marrow's daily output of cells. If this is so, the life span of a reticulocyte is about one day. From the data of Crosby and Akeroyd (Table III), one might expect that a maximum output of reticulocytes, and therefore a maximum reticulocyte count, would be about seven times the normal—that is, about 350,000 cells per cubic millimetre. The data in Figure II provide support for this view. The patient was a young woman who had been in

TABLE III.

Data Showing Compensatory Increase in Marrow Output Maintaining Normal Hæmoglobin Concentration in Spite of Greatly Shortened Red-Cell Survival.[1]

Patient's Condition.	Hæmoglobin Value. (Grammes per 100 Ml.)	Red-Cell Life Span. (Days.)	Marrow Output per Day.		Fæcal Urobilinogen Observed.[2] (Mgm.)
			Red Cells. (Ml.)	Hæmoglobin. (Grammes.)	
Familial hæmolytic anæmia.	13·5	11	120·0	40·0	760 (1400)
Familial non-spherocytic hæmolytic anæmia.	11·0	12	136·0	45·0	1300 (1575)
Normal (calculated).	—	120	18·8	6·25	50 to 250

[1] From Table I, Crosby and Akeroyd (1952).

[2] The figures in parentheses are calculated from the hæmoglobin breakdown.

good health immediately prior to the onset of an acute and severe hæmolytic anæmia, and who has remained in good health for three years since this was cured by splenectomy 21 days after the onset of her illness. No cause was found for the anæmia, but it was clearly hæmolytic. No abnormal antibodies could be demonstrated, cell fragilities were normal and there was no family history of anæmia or jaundice. The important point, however, is that her physical state before, during and after the illness

TABLE IV.

Maximal Reticulocyte Response in Pernicious Anæmia under Treatment.

From Whitby and Britton (1957), Table IX.		Calculated Number of Reticulocytes per C.mm.[1]
Initial Red-Cell Count. (Millions per C.mm.)	Peak Reticulocyte Count.	
0·5	55%	550,000
1·0	35%	520,000
1·5	22%	440,000
2·0	14%	350,000
2·5	8%	240,000
3·0	2%	60,000

[1] The figures are calculated according to the method of Minot *et alii* (1928), to allow for the slight increase in red-cell count by the time the reticulocyte peak is reached.

suggested that there was no underlying constitutional disease, and that her marrow response should have been normal. It is interesting, therefore, that her reticulocyte counts throughout the illness should have approximated closely the estimated maximal response. The progressive anæmia indicated that the rate of cell destruction was in excess of the maximal regenerative capacity of the marrow.

In Figure III are shown the maximum reticulocyte counts of 27 patients with reticulocytosis due to various types of hæmolytic anæmia. In all but five the count falls between 50,000 and 500,000 per cubic millimetre. The five higher values ranged from 640,000 to 1,674,000 per cubic millimetre. In this last patient, over a period of 14 days four reticulocyte counts were made, and all were above 1,300,000 per cubic millimetre. The red blood cell count remained steadily at about 2,700,000 per cubic millimetre. Either the marrow was producing over 1,000,000 reticulocytes per cubic millimetre per day, or the reticulocytes were surviving longer than the postulated 24 hours, and the counts represented three or four days' supply of reticulocytes.

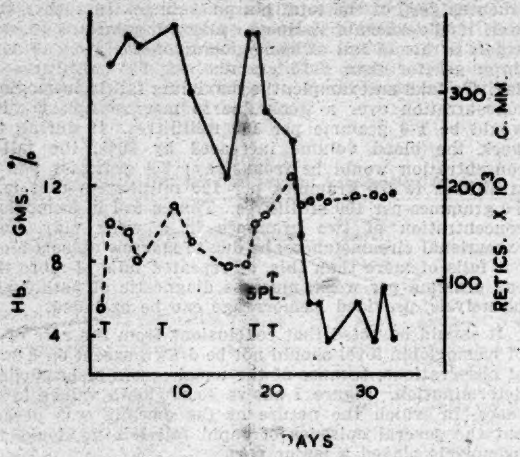

FIGURE II.

Reticulocyte counts (continuous line) and hæmoglobin concentration (broken line) in a young woman with acute hæmolytic anæmia of undetermined cause. The condition was cured by splenectomy. The reticulocyte response was probably maximal.

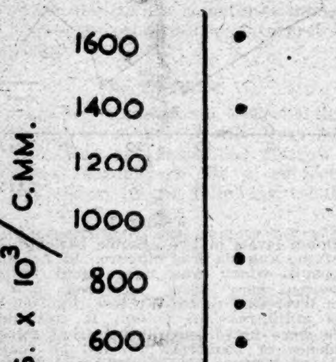

FIGURE III.

Maximal recorded reticulocyte response in 27 patients with hæmolytic anæmia of various ætiologies.

To refer again to Table IV, the reticulocyte response in a patient with pernicious anæmia responding maximally to adequate liver therapy is of the same order as in hæmolytic anæmia. Of the 48 patients studied by Minot *et alii*, with initial red-cell counts below 1,500,000 per

cubic millimetre, the smallest reticulocyte peak was 290,000 and the greatest 830,000 per cubic millimetre.

By contrast, in the presence of a hæmolytic anæmia, the absence of a reticulocyte response of this degree and especially the absence of any reticulocytes indicate associated marrow deficiency. The data in Table V are from a patient in whom there was undoubted hæmolysis. In the early stage of her illness there was a partial but submaximal reticulocyte response; but this gradually faded, and in spite of splenectomy she died 11 months after the onset of illness. Autopsy showed complete

Table V.

Data Indicating Marrow Failure in a Patient with Pathologic Hæmolysis (B. of Figure I).

Date.	Hæmoglobin Value. (Grammes per 100 Ml.)	Leucocytes per C.mm.	Platelets per C.mm.	Reticulocytes per C.mm.
1952:				
November 4 ..	5·0	2000	19,000	9600
November 12 ..	5·4	2400	6000	36,000
November 25 ..	3·9	1950	—	39,000
December 12 ..	9·0	1800	17,000	14,000
1953:				
January 13 ..	11·0	1450	—	18,000
January 30 ..	4·7	950	76,000	7000
February 17 ..	6·8	600	11,000	10,000
March 6 ..	9·6	600	27,000	—
March 12 ..		Splenectomy.		
March 18 ..	7·7	4350	30,000	—
March 19 ..	9·2	10,300	18,500	—
March 26 ..	6·8	4800	40,000	—
April 1 ..	6·3	2400	30,000	—
April 5 ..		Patient died.		

marrow aplasia. Submaximal or absent reticulocyte response is of bad prognostic significance in a patient with hæmolytic anæmia, but may sometimes be due to an associated hypersplenic syndrome, and both the anæmia and regenerative failure may respond to splenectomy. The data in Table VI are from such a patient.

Table VI.

Hæmolytic Anæmia and Pancytopenia with Recovery after Splenectomy (Patient A. of Figure I); no Primary Cause for the Splenomegaly was Found.

Date.	Hæmoglobin Value. (Grammes per 100 Ml.)	Leucocytes per C.mm.	Platelets per C.mm.	Reticulocytes per C.mm.	Serum Bilirubin Content. (Mgm per 100 Ml.)
February 15, 1954	8·2	2750	69,000	10,000	0·5
February 24, 1954	5·9	1750	44,500	8000	—
February 25, 1954		Corticosteroid therapy commenced.			
March 5, 1954	9·6	4000	43,000	17,400	—
March 16, 1954	6·3	2400	150,000	—	—
March 22, 1954	7·7	2050	165,000	12,000	—
March 26, 1954	12·0	3350	245,000	22,000	—
April 23, 1954	7·7	7300	185,000	—	—
May 31, 1954	6·3	2700	160,000	15,000	—
June 22, 1954	10·0	4800	—	16,000	0·4
July 13, 1954			Splenectomy.		
August 19, 1954	9·7	11,600	—	18,000	—
September 24, 1954	10·4	11,400	—	—	—
December 1, 1954	11·8	12,300	300,000	19,000	—
February 2, 1955	12·9	15,200	—	—	—
November 11, 1955	13·0	8100	—	—	—
October 22, 1956	15·2	10,700	265,000	—	—

Pigment Changes.

Increased bilirubinæmia of moderate degree is usually, but by no means invariably, present with pathological hæmolysis. The blood level depends on the balance between rate of formation and rate of excretion by the liver. One gramme of hæmoglobin gives rise to approximately 35 milligrammes of bilirubin, which is converted to 35 milligrammes of urobilinogen. The normal daily hæmoglobin breakdown is about 7·5 grammes, and the normal excretion of urobilinogen should thus be 260 milligrammes. Observed figures have varied from 40 to 280 milligrammes (Watson and Bilder, 1937) and from 22 to 121 milligrammes (Maclagan, 1946). The normal liver thus has little difficulty in excreting 260 milligrammes of bilirubin per day, but it is not clear at what daily load it begins to fail. In Crosby and Akeroyd's patient, who had normal hæmoglobin levels but hæmoglobin breakdown at the rate of 40 grammes per day, the bilirubin levels of serum varied from 1·8 to 4·0 milligrammes per 100 millilitres. It is thus apparent that with a normal marrow and normal liver, jaundice will appear before anæmia. This is consistent with the aphorism "more jaundiced than sick", often applied to the child with familial hæmolytic anæmia.

In Figure IV, paired readings of bilirubin levels and reticulocyte counts have been correlated. The data are taken from the records of 29 patients with various types of hæmolytic anæmia from the Royal Prince Alfred

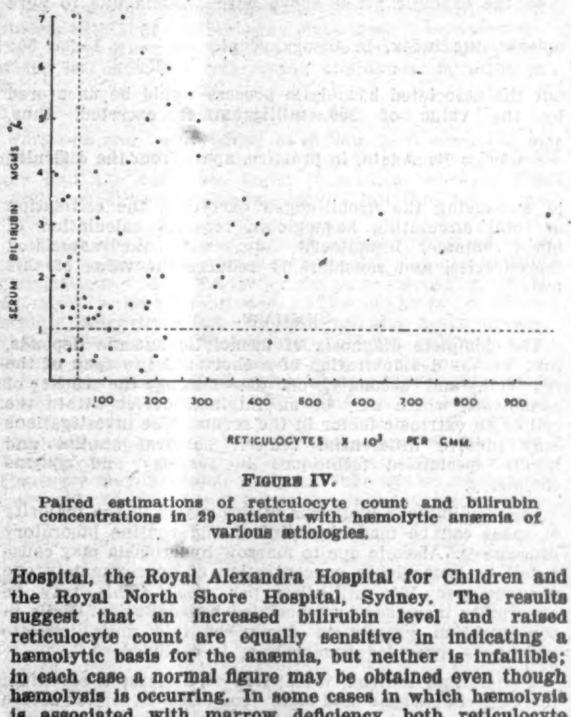

Figure IV.

Paired estimations of reticulocyte count and bilirubin concentrations in 29 patients with hæmolytic anæmia of various ætiologies.

Hospital, the Royal Alexandra Hospital for Children and the Royal North Shore Hospital, Sydney. The results suggest that an increased bilirubin level and raised reticulocyte count are equally sensitive in indicating a hæmolytic basis for the anæmia, but neither is infallible; in each case a normal figure may be obtained even though hæmolysis is occurring. In some cases in which hæmolysis is associated with marrow deficiency, both reticulocyte count and bilirubin levels may show no increase.

As an increased rate of bilirubin production due to hæmolysis may be compensated by increased rate of excretion, the process should be reflected by an increase in the excreted end products of bilirubin breakdown.

The wide variation found in normal subjects and discrepancies in values found in patients suffering from hæmolytic anæmia reduce the value of this test, so that in the borderline and difficult case it contributes little. Other limitations include the difficulty of daily stool collections, technical difficulties of the estimation associated particularly with the use of an arbitrary colour standard, the fact that some urobilinogen may be derived from myoglobin and pigments other than hæmoglobin, and doubts as to the completeness of conversion of the bilirubin and the quantity of urobilinogen reabsorbed.

If an anæmia is due to marrow hypoplasia alone and the marrow production is about one-third of normal, after equilibrium has been established the total hæmoglobin mass will remain at 250 grammes and the hæmoglobin concentration at 5·0 grammes per 100 millilitres. The cell

survival will be the normal 100 days, and each day 2·5 grammes of hæmoglobin will be destroyed. The urobilinogen output would theoretically be 75 milligrammes daily. With this degree of marrow hypoplasia, an increase in urobilinogen excretion, say to 150 milligrammes per day, must indicate considerable associated hæmolytic disease, and yet the total urobilinogen excretion is within the normal range.

This source of error can be uncovered if an excretion index is used. Thus:

$$\frac{\text{Daily fæcal excretion of urobilinogen (mgm.)} \times 100}{\text{Total hæmoglobin mass (gm.)}}$$

For example: $\frac{250}{750} \times 100 = 33\frac{1}{3}$.

In practice, Miller *et alii* (1942) found the index in normal subjects to be between 10 and 20 milligrammes per 100 grammes of circulating hæmoglobin.

In the example given above with anæmia due to pure aplasia, the index, in theory, would be $\frac{75}{250} \times 100 = 30$; but the associated hæmolytic process would be uncovered by the value of 150 milligrammes excreted, thus, $\frac{150}{250} \times 100 = 60$. Again, in practice, apart from the difficulty of measuring the urobilinogen excretion, the estimation of total circulating hæmoglobin requires calculation of blood volume, hæmatocrit, etc., with the associated inaccuracies, and considerably reduces the value of this test.

Summary.

The complete diagnosis of hæmolytic anæmia depends, first, on the demonstration of a shortened life span of the red cell, and secondly, on determining the cause of hæmolysis, which may be an intrinsic defect within the cell or an extrinsic factor in the serum. The investigations may involve differential red-cell survival studies and highly specialized techniques in serology and enzyme chemistry.

The preliminary diagnosis of hæmolysis in the majority of cases can be made by clinical and routine laboratory procedures. Anæmia due to marrow hyperplasia may cause a fall in hæmoglobin concentration of approximately one gramme per 100 millilitres per week. This may be apparently increased by associated hæmodilution. Falls in concentration greatly in excess of this must indicate hæmolysis, provided hæmorrhage is excluded.

The normal marrow is capable of at least a sevenfold increase in output and may compensate for a severe hæmolytic process, thus maintaining a normal blood count. In this case hæmolysis may be indicated by an increased reticulocyte count. There are normally 50,000 reticulocytes per cubic millimetre, and evidence is quoted to suggest that this represents the normal daily supply of red cells. A sevenfold increase in reticulocytes to about 350,000 per cubic millimetre is usually seen when severe hæmolysis is associated with a normal marrow.

The serum bilirubin content is usually increased to 3·0 or 4·0 milligrammes per 100 millilitres. This increase may not occur if excretion is rapid. In some cases hæmolysis may occur in the absence of either reticulocytosis or hyperbilirubinæmia. Failure of a reticulocyte response is a bad prognostic sign.

Determination of daily urobilinogen excretion is of little use in demonstrating hæmolysis, and while calculation of a hæmolytic index is theoretically sound, it has many practical limitations.

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PULMONARY EMBOLISM AND PULMONARY INFARCTION.[1]

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The reason for discussing once again the subject of pulmonary embolism and pulmonary infarction is not because there is much new information to bring to your notice but rather because it is a common problem met in surgical, obstetrical and medical wards as well as in general practice. In spite of the fact that, according to some often-quoted authorities, it is the commonest acute respiratory disorder in a general hospital, even exceeding in frequency pneumonia and lung cancer, its clinical features are not widely enough recognized, and the value of the ancillary aids, especially radiography and electrocardiography, are not always appreciated.

Not so long ago the occurrence of pulmonary embolism was regarded as a stroke of bad luck, somewhat like the visitation of God of centuries ago, unexplained and humbly accepted as inevitable. Indeed, when one recalls the case of a young doctor's wife who on the tenth day after confinement, on her way home from maternity hospital, suddenly was stricken by lethal pulmonary embolism, such a fatalistic view did not appear altogether unreasonable. Fortunately, knowledge accumulated during the last decade or two has brought to light information concerning pre-

[1] Based on a lecture given in Canberra on April 18, 1958, during the seventh annual post-graduate week of the Federation of Country Local Associations of New South Wales.

disposing factors which allow a more realistic approach to this problem.

Incidence.

The medical literature quotes varying figures for the incidence of pulmonary thrombo-embolic disease. Brooks (1952) states that pulmonary embolism causes 2% to 3% of all hospital deaths, less than half of which are diagnosed clinically.

With the assistance of Dr. E. S. Finckh, Department of Pathology, University of Sydney, and Dr. B. H. Coombes, from the Pathology Department, Sydney Hospital, the incidence of pulmonary embolism and infarction in two Sydney teaching hospitals during the past 12 months was studied. A total of 772 autopsies were reviewed, and 37 instances of pulmonary thrombo-embolic disease were discovered, the incidence being approximately 5%. The number of cases of pneumonia and bronchial carcinoma seen during the same period was considerably lower. In our series there was no significant sex difference. One of the most interesting points to emerge from our survey was that 33 of the 37 patients were 50 years of age or older; in other words, almost 90% of all fatal pulmonary emboli or infarctions occurred in the older age group. The four younger patients are worth more comment: a youth of 18 years died from osteomyelitis, pyæmic abscesses and pulmonary infarction; a woman, aged 36 years, died suddenly two days after mitral valvotomy; a female, aged 41 years, who died from recurrent subacute bacterial endocarditis and perforated aortic valve, had multiple pulmonary infarctions. Perhaps most amazing of all was the case of a woman, aged 36 years, who was admitted to hospital for investigation of headaches, for which no cause was discovered, and who died suddenly and unexpectedly whilst in bed. At autopsy, deep vein thrombosis in the left calf and a large ante-mortem thrombus in the right lower lobe pulmonary artery were found.

In our series, 16 of the 37 patients suffered primarily from cardiac conditions. In 12 cases the underlying disease was acute or chronic myocardial infarction. The remaining four patients with cardiac disease, all females, suffered from valvular heart disease, two from mitral stenosis, one from aortic valve disease, combined stenosis and incompetence, and one from subacute bacterial endocarditis of the aortic valve.

More than one-third of our patients with pulmonary thrombo-embolic disease, 14 of the 37, suffered from a malignant condition. Four of these patients had carcinoma of the cervix, uterus or ovaries, and three had gastro-intestinal malignant disease. The other seven cases were different conditions, including one Grawitz tumour complicated by femoral vein thrombosis and sudden death, the primary condition being quite silent and unsuspected until autopsy.

It is perhaps a sobering thought that 90% of fatal pulmonary infarcts occur in the group over 50 years of age, and that in 80% the victims suffer from heart disease or malignant disease, the "two great killers" of our age. This could mean that elderly patients, or those suffering from heart disease and malignant disease, are especially prone to pulmonary embolism and pulmonary infarction, or else that patients who do not suffer from otherwise fatal conditions do not fare so badly and therefore do not come to autopsy. If the latter supposition is true, and there is some clinical evidence to suggest that that is so, the credit may go to our present-day methods of treatment, or else the natural history of thrombo-embolic pulmonary disease may be less serious than is normally thought.

Pathology.

The pathology of the subject remains somewhat confused in spite of, or perhaps because of, the so-called classical writings of Rokitansky, Virchow, Welch and Aschoff. It appears preferable to discuss pulmonary embolism and pulmonary infarction as one entity, stressing their cause and effect relationship rather like coronary thrombosis and myocardial infarction. This concept, of course, in no way denies the fact that massive pulmonary embolism may cause sudden death before any evidence of pulmonary infarction can be demonstrated at autopsy, nor does it of course explain the not infrequent pathological impasse of not being able to demonstrate the embolism in a case of pulmonary infarction.

Many pathologists have produced evidence that a number of pulmonary infarcts are not due to emboli but are the result of primary thrombosis in the pulmonary arteries or their major branches. The occurrence of pulmonary artery thrombosis appears established, especially complicating long-standing heart disease. Two such cases were found in our material mentioned above. Yet the majority of instances of thrombo-embolic disease of the lesser circulation may be accepted as being due to embolization from peripheral veins.

The majority of pulmonary infarcts are found in the lower lobes; in only three out of the 37 cases studied at autopsy was infarction confined to the upper lobes, a point well worth bearing in mind when considering the differential diagnosis in an individual case. In two-thirds of our material, pulmonary infarction was multiple; in subjects with single infarcts the right lower lobe was somewhat more often involved than the corresponding lobe on the left side, the ratio being approximately three to two.

Predisposing Factors.

Surgeons and obstetricians have long been conscious of pulmonary embolism. Yet in a general hospital more than half the cases are found in medical wards. The so-called medical predisposing factors fall into four main groups.

1. Heart disease. Over 10% of patients admitted with cardiac disease of diverse ætiology develop thrombo-embolic complications. The frequency in our autopsy material has already been mentioned. The majority of these patients suffer from ischæmic and valvular heart disease. White (1940) states that nearly half the patients with chronic congestive heart failure and nearly one-third of all patients with mitral valve disease have pulmonary thrombo-embolic complications. Pulmonary embolism and infarction are particularly liable to occur with chronic pulmonary congestion. The clinical signs of this complication may then be relatively unspectacular, and only at autopsy may it become apparent that one of the factors responsible for the chronicity of the pulmonary congestion was the presence of multiple pulmonary infarcts. The incidence of this complication is also higher in the presence of atrial fibrillation; the source of the emboli may then be found in right auricular thrombi.

2. Malignant disease. The association of thrombo-embolic disease with malignant disease has been known for over a century, since Trousseau, who himself was thus afflicted, described the relationship. Visceral carcinoma should be suspected in any patient over 40 years of age suffering from unexplained recurrent thrombo-phlebitis, especially of the migrating variety. However, in actual practice the search in this type of patient for a hidden malignant disease with full radiological and endoscopic examinations is not often rewarding, and one feels reluctant to submit such a patient to a full battery of tests unless some other clinical pointer is available.

3. Thrombo-phlebitis. Pathological material demonstrates that over 60% of pulmonary emboli are associated with deep venous thromboses of the extremities or of the pelvis. The differentiation between thrombo-phlebitis and phlebo-thrombosis once popular in the United States is of doubtful value. Superficial thrombo-phlebitis is very frequently associated with deep venous thrombosis and may give rise to pulmonary emboli. The same complication occurs occasionally after sclerosing treatment for varicose veins.

4. Prolonged immobilization. Any patient who is put to bed is a candidate for thrombo-embolic accidents including pulmonary emboli. The older the patient, the shorter the period of immobility which may be regarded as potentially dangerous. The possible ill effects of a stay

in hospital have already been referred to. A number of deaths due to pulmonary emboli were described during the last war amongst old people confined to overcrowded air-raid shelters sleeping on deck-chairs and with a wooden bar behind their knees. A typical case was seen a short while ago. A man, aged 74 years, who had never previously been ill, was run over by a police motor-cycle outside Wynyard station in Sydney, sustained a fractured pelvis, had to be immobilized in a pelvic sling and a fortnight later suddenly developed right pleural pain and hæmoptysis. X-ray examination of the chest revealed right basal pulmonary infarction. Similar cases have been seen in the special ward for elderly females with fractured femora at the Prince of Wales division of Sydney Hospital, in spite of the fact that the whole aim of the orthopædic management there is early ambulation.

A pre-thrombotic state has been recognized for some time. It occurs after extensive surgical procedures, confinements, etc., especially in patients who are dehydrated and compelled to periods of prolonged bed rest, and whose respiration is shallow for one reason or another. Alterations in the coagulation mechanisms have been demonstrated with shortened clotting time and increased platelet stickiness. There are also changes in serum protein levels and increases in the fibrinogen fractions. Attempts by Cummine and Lyons (1948) to demonstrate an abnormal fibrinogen, fibrinogen B, have not been generally accepted.

Clinical Manifestations.

The clinical material may be divided into two groups: (i) Anticipated pulmonary embolism. This has largely been discussed under the heading of predisposing factors. (ii) Unheralded pulmonary embolism. This is a syndrome likely to be misdiagnosed and thus inadequately treated. Careful analysis of the clinical features and proper interpretation of ancillary findings should reduce the number of mistaken diagnoses.

The syndrome of pulmonary embolism may at first sight resemble the clinical picture of myocardial infarction. The patient complains of a central chest pain of sudden onset, with acute breathlessness and in severe cases complicated by shock and vasomotor collapse. If the embolism is large, this stage may be rapidly fatal, the well-known "call-for-a-bed-pan-and-die" sequence, more often seen by resident medical officers than by the visiting medical staff.

Only the non-fatal pulmonary emboli go on to the syndrome of pulmonary infarction. The clinical features of this condition may be described under the headings of major or pulmonary triad and minor or non-specific triad. The major consists of pleural pain in 90% of cases, hæmoptysis present in about 50% of cases, and cough without purulent sputum. The absence of purulent sputum in patients with pleurisy and radiological shadows should always suggest a vascular rather than an infective ætiology. Another suggestive feature of this major triad is the recurrence of so-called attacks of pleurisy, often involving both sides. The minor non-specific triad consists of pyrexia, tachycardia and icterus. The first two, pyrexia and tachycardia, may precede the pulmonary symptoms, and examination of the legs at that stage in a predisposed subject often reveals evidence of deep calf vein thrombosis, calf tenderness, pain on dorsiflexion of the foot (Homans's sign), œdema, etc. Icterus occurs only in patients with heart disease and chronic congestive failure. It appears to be due to hæmolysis in the area of infarction and inability of the congested liver to handle the extra bilirubin.

Complications.

Massive pulmonary embolism occurs when 60% of the pulmonary circulation is occluded, causing gross overdistension of the right ventricle and sudden fall in cardiac output. It has been estimated that death occurs when 80% of the pulmonary artery is blocked. Mechanical obstruction has not been a satisfactory explanation for all fatal cases and therefore other mechanisms have been postulated, such as reflex cardiac inhibition mediated via the vagus nerve, as demonstrated in experimental animals, or possibly a humoral mechanism, the one most recently investigated involving 5-hydroxytryptamine (serotonin).

A pleural reaction with a small effusion occurs very frequently; in about half the cases the effusion is hæmorrhagic. Rarely, massive unilateral recurrent effusion is due to pulmonary infarction, and in such cases the difficult differential diagnosis from tuberculosis and neoplasm may be suggested by a negative result to a parietal pleural needle biopsy. Superadded infection of a pulmonary infarct may lead to lung abscess or occasionally to empyema. Other complications include recurrence of thrombo-embolic phenomena and the development of congestive cardiac failure and arrhythmias, usually in patients with underlying heart disease. Finally, a rare but interesting group of patients should be mentioned who develop obstructive pulmonary hypertension and chronic pulmonary heart disease as a result of recurrent silent pulmonary emboli. These patients finally present the clinical picture of primary pulmonary hypertension, except that instead of pursuing a relentless, progressive, downhill course, their condition may be halted or even reversed by long-term anticoagulant therapy. Three such patients were recently described by Davison *et alii* (1956).

Differential Diagnosis.

Pulmonary embolism in the acute stage is most likely to be confused with myocardial infarction, possibly dissecting aneurysm or other vascular catastrophes. Pulmonary infarction has been mistaken for a number of lung conditions, including various types of pneumonia, atelectasis (especially occurring post-operatively), tuberculosis, bronchial carcinoma and lung abscess. The difficulty of differentiating primary pleural effusion has already been mentioned.

Ancillary Aids to Diagnosis.

The main ancillary aids in the diagnosis of pulmonary embolism and pulmonary infarction are radiology and electrocardiography. In spite of extensive investigations, no diagnostic test has yet been elaborated based upon clotting changes and serum protein alterations observed as part of the pre-thrombotic stage. In the differential diagnosis from cardiac infarction the serum transaminase reaction promises to be of some help. The serum transaminase level (S.G.O.-T. assay) is never greatly raised in pulmonary infarction, but is almost invariably increased whenever there is myocardial necrosis. An investigation to verify the value of this relatively simple laboratory test is at present being undertaken at Sydney Hospital with the cooperation of Dr. M. A. Mishkel.

Radiology.

Some radiological abnormality can be demonstrated in nearly 90% of cases of pulmonary infarction. Short (1951) excellently reviewed the subject and stated that the infarct shadow could be seen in 70%. It may take the form of an area of consolidation or merely be represented by basal clouding or a costo-phrenic opacity. The classical triangular shadow with the base towards the periphery and the apex pointing towards the hilum is only rarely seen. When healing occurs, a linear shadow representing the scar of the old infarct may be produced. The occurrence of a pleural reaction in 50% of cases and the early appearance of elevation of the diaphragm on the side of the lesion in 30% have been stressed by Short (1951). X-ray examination within 12 hours of onset may fail to reveal any abnormality. Westermark (1938) described an area of increased translucency due to pulmonary ischæmia as an early sign of pulmonary embolism; we have not yet been able to confirm the value of this sign. Infarct shadows may disappear within a week, but occasionally persist for up to two months. Linear shadows may remain as permanent scars.

If radiological examination fails to reveal the expected confirmatory evidence of pulmonary infarction, the infarct shadow may actually be hidden behind the heart or diaphragm. Reexamination with the addition of lateral

views may be helpful. Difficulty in the radiological diagnosis can also be expected in the presence of marked pulmonary congestion and when a large pleural effusion is present. In a case with negative findings on X-ray examination, the examination may have been carried out too soon or too late to demonstrate the infarct; this shows again the importance of frequent reexaminations. Inadequate technique not infrequently is responsible for radiological failures; the patients are often too sick for anything but a "snatch portable X-ray". During the recovery phase, fluoroscopy and occasionally tomography will be of value in the radiological diagnosis.

Electrocardiographic Changes.

The classical electrocardiographic changes of pulmonary embolism due to acute right ventricular strain are seen only in 10% of cases. Recently, however, the importance of relatively minor positional changes in the confirmatory diagnosis of pulmonary embolism has been appreciated, so that some observers now put the incidence of suggestive, if not diagnostic, changes as high as 70% (Israel and Goldstein, 1957). Serial tracings reveal transient right axis deviation, vertical shift of the electrical position of the heart and, above all, clockwise rotation around the longitudinal axis, all due to sudden overdistension of the right ventricle. These positional changes are responsible for the appearance of an *S* wave in lead I, *Q* wave in lead III, with inverted *T* wave in lead III, occasionally transmitted to aVF, the appearance of an *R* wave in aVR and a tall *P* wave, the *P* pulmonale. With these there is invariably a shift of the transitional zone in the multiple chest leads towards the left. It is when these positional changes are associated with *T* wave inversion in the right chest leads V1 to V4 or with a right bundle branch block that the so-called classical electrocardiographic pattern of pulmonary embolism is produced. Transient ischæmic changes with *S-T* segment depression in left ventricular surface leads and various arrhythmias may complicate the electrocardiographic diagnosis.

Treatment.

Fortunately, better understanding of pulmonary embolism and pulmonary infarction has also led to improved management, from both the prevention and the treatment points of view. The key to successful prophylaxis lies in the appreciation of the predisposing factors. Prompt treatment of peripheral vein thrombosis with anticoagulant drugs, early post-operative ambulation, avoidance of dehydration and deep-breathing exercises have greatly reduced the incidence of thrombo-embolic complications. Prophylactic anticoagulant treatment may also be instituted for subjects considered particularly prone to such accidents within 48 hours of most surgical procedures. It is indeed worth while remembering that some Scandinavian surgeons perform mitral valvotomy in patients with a previous history of embolic events, under long-term anticoagulant cover, and have apparently not been troubled by undue bleeding complications. This example is quoted not because we advise such preoperative preparation for mitral valvotomy, but to illustrate how familiarity with a particular line of treatment leads to confidence and wider application. On the other hand, prophylactic bilateral femoral vein ligation, at one stage popular in the United States, is now only of historical interest.

The treatment of established pulmonary embolism consists first of all of relief of pain, and for this purpose morphine in adequate dosage still has no equal. To inhibit vagal reflexes, atropine is a useful drug in pulmonary embolism, in contrast to myocardial infarction and pulmonary œdema, in which atropine may do more harm than good on account of its tachycardiac effect. In the United States and on the Continent, papaverine given intravenously is advocated, but it has not been demonstrated to be more effective than the morphine and atropine régime. If shock is marked and the systolic blood pressure has dropped to 90 millimetres of mercury, pressor-amines may be life-saving, the most potent still being an intravenous infusion of nor-adrenaline, the concentration of the drug and the rate of drip being critically adjusted to maintain blood pressure. The use of nor-adrenaline supplemented by hydrocortisone in desperate cases has undoubtedly saved lives in massive pulmonary embolism, more so even than in myocardial infarction.

Every patient with thrombo-embolic disease should be treated with anticoagulant drugs unless some strong contraindication is present, such as active peptic ulcer, a bleeding tendency, and advanced hepatic or renal insufficiency. Routine treatment consists of intermittent intravenous injections of heparin, starting with 10,000 units, followed by 5000 units every four hours for approximately 48 hours, by which time the phenindione given orally, commenced at the time of the first heparin injection, has usually depressed the prothrombin concentration to therapeutic levels. Oral anticoagulant therapy is continued until the patient is once again ambulant and for a minimal period of two weeks after the last thrombo-embolic episode. The drawback of phenindione therapy is that laboratory facilities for prothrombin estimations are essential, otherwise the drug may be useless, if given in inadequate amounts, or dangerous if given too enthusiastically. The maintenance dose of phenindione may vary from 25 milligrammes to 400 milligrammes per day and has to be established for each patient individually. If no laboratory facilities are available, it is probably better to use heparin only, if necessary even on a twelve-hourly basis and given intramuscularly, with careful supervision and early recognition of excessive bruising to avoid dangerous overdosage.

Conclusions.

Pulmonary embolism and pulmonary infarction are amongst the commonest acute respiratory disorders seen in general hospital wards. The predisposing factors, with special reference to heart disease and malignant disease, are discussed. The value of radiology and electrocardiography as ancillary diagnostic aids is stressed. Present-day management, both preventive and therapeutic, is reviewed.

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HALF A CENTURY OF PROGRESS IN RADIO-DIAGNOSTIC PROTECTION.[1]

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THIS paper is a review of the growth of our knowledge of the dangers of X rays, and of the protective measures taken to overcome them. It is also an attempt to put these hazards into their proper perspective. Before com-

[1] Read at a meeting of the Section of Radiology and Radiotherapy, Australasian Medical Congress (B.M.A.), Tenth Session, Hobart, March 1 to 7, 1958.

mencing, I would like to stress that we are all subjected to natural radiation all our lives from cosmic rays formed in space, from radioactive rocks in the ground and in our buildings, and from decaying radioactive elements in our own bodies. Life has evolved against this background.

I intend to treat this subject from an historical angle. I have divided the history of radiation into four phases, namely those of blissful ignorance, somatic martyrdom, genetic hazard, and the hopeful future. These phases were merely facets of the problem as they became apparent, but, of course, they have always coexisted.

Blissful Ignorance.

It is often overlooked that the whole history of radiation can be compressed into little more than half a century, that is within the lifetime of many of the members of this Congress. X rays were discovered by Röntgen in Germany on November 8, 1895; this preceded the discovery of radium by a couple of years. The news of the discovery reached the United Kingdom in January of the following year, and the first X-ray photographs were taken in that country in the same week. The conservative professions of medicine and the law early recognized their value, and X rays were first used medico-legally in March, 1896, that is within four months of their discovery. The British Army dispatched two X-ray sets to their surgeons in the Nile Valley a couple of months later. You will notice that all this happened within six months of Röntgen's discovery, so that some of the dangers were obvious early. In November, 1897, Sylvanus Thompson described X-ray dermatitis and epilation in a lecture, and in the following year the Röntgen Society set up a committee to investigate possible hazards. In the same year (1898) Pierre and Marie Curie discovered radium.

Knowledge of the more serious effects accumulated more gradually, and it was not until the 1920's that many of the early workers in this field, who had received very high doses of radiation, began to die of malignant diseases and aplastic anæmia. There is a memorial in Hamburg to these radiation martyrs, which serves as a grim reminder of the fate of those who fail to treat these painless invisible rays with proper respect. In 1921, the British X-ray and Radium Protection Committee was set up, and recommended the first tolerance dose for workers with radiation. An international commission in 1954 reduced this considerably, but monitoring shows that most workers with ionizing radiation receive much less than the recommended dose.

Before considering two of the somatic effects, I shall deal briefly with the remaining historical background. Muller in 1927 was the first to demonstrate that X rays could cause mutations. Little notice was taken of this, except by those especially interested in the subject, until 1945, when the first atomic bomb was exploded. Since then there has been increasing interest throughout the world in the possible genetic effects of radiation.

Somatic Martyrdom.

There are many somatic effects of radiation, but I shall discuss only two, which are much in the public eye at the moment, namely the production of leukæmia and the effects on the fœtus.

There is no doubt that X rays can produce leukæmia, and that the incidence of this disease has approximately trebled in Western countries in the last 30 years. However, as far as I can ascertain, there is no evidence to suggest that these facts are related. I now wish to consider the incidence of leukæmia developing after deep X-ray therapy for ankylosing spondylitis, as quoted from the Medical Research Council's report (Table I). Thirteen thousand patients were treated and followed for up to 20 years, and amongst these were 37 deaths from leukæmia. What interests me about these figures is the low incidence of leukæmia in those patients receiving less than 500*r*, which is a dose far in excess of that used in diagnostic work. Evidence from other sources such as the experimental irradiation of animals, and the incidence of leukæmia in radiologists and survivors of atomic bomb explosions confirms that X rays cause leukæmia, but the dose required is very much larger than that used in radiodiagnosis. Witts, in a recent article (1957), pointed out that the death rate from leukæmia in the series of patients treated for ankylosing spondylitis by deep therapy as mentioned above was three per 1000, and he compared it with the mortality rate of 13 per 1000 for interval partial gastrectomy in the best hands, which is four times as great. Surely deep therapy for ankylosing spondylitis is much less harmful than interval gastrectomy? A certain mortality or morbidity is accepted with many forms of medical treatment and even with some

TABLE I.

The Incidence of Leukæmia Developing after Deep X-Ray Therapy for Ankylosing Spondylitis in 13,000 Patients up to 20 Years Later.

Spinal Marrow Dose (*r*).	Number of Cases of Leukæmia.	Incidence per Year per 10,000 Patients Treated.[1]
0	—	0·8
Less than 500 ..	2	2·2
500 to 999 ..	8	4·1
1000 to 1499 ..	8	4·2
1500 to 1999 ..	8	11·3
2000 to 2749 ..	6	13·0
Over 2750	5 37	17·6

[1] The incidence of leukæmia in an unirradiated population is 0·8 per 10,000 *per annum*.

investigations, so why not with the use of X rays? Deaths have been reported from injections of penicillin, but this has not caused an outcry against its use.

I would like now to turn to the possible effects on the fœtus. Much interest in this was aroused by a preliminary communication by Stewart *et alii* in 1956 about the possible production of malignant disease by ante-natal irradiation of the fœtus. This led to many wild statements in the lay Press. Just what did Stewart *et alii* show? They analysed 547 cases out of a total of 1500 of fatal malignant diseases in children under the age of 10 years (Table II). Of these

TABLE II.

Malignant Disease and Pre-Natal X-ray Examination.
(*After* Stewart *et alii*, 1956.[1])

Maternal Region Radiologically Examined.	Number of Cases of Leukæmia.	Number of Cases of Other Malignant Diseases.	Total.
Abdomen	42 (24)	43 (21)	85 (45)
Other	25 (23)	33 (32)	58 (55)

[1] Control figures are in parentheses.

547 malignant diseases, only 40 could possibly have been due to ante-natal irradiation—surely a minor proportion when compared with over 500 of unknown cause. As Witts (1957) pointed out, these 40 deaths must also be set against the annual United Kingdom statistics of 400 maternal deaths in childbirth, 16,000 stillbirths and 10,000 neonatal deaths. This puts Stewart's work in its proper perspective; when there is reason to believe an ante-natal X-ray examination could save a mother or fœtus it must be used without hesitation. In passing, evidence from deep X-ray therapy and from the Hiroshima atomic bomb explosion indicates that heavy irradiation of the fœtus can cause microcephaly, but, as far as I can discover, none of these microcephalic children has as yet developed leukæmia.

Genetic Hazard.

As previously mentioned, it has been realized since 1927 that X rays cause genetic mutations, and I will just outline briefly a few fundamental facts about mutations before considering what examinations are likely to cause the greatest damage. Naturally, these remarks apply only

neopl no neopl
Stewart fetal irrad 178 93
Total 1299 1299

to patients before or during the reproductive ages. It must not be forgotten that spontaneous mutation is occurring all the time, and is the fundamental mechanism of evolution. Once a mutation has been produced, it is passed on unchanged to the offspring, until it is eliminated by the death of the person carrying it. Virtually all mutations are harmful, and, depending on whether they are dominant or recessive, they may persist for one or many generations. There is therefore a balance between the rate of production of new mutations and their elimination by genetic death. Modern medicine has undoubtedly upset this balance by preventing many genetic deaths, whilst X rays are a further disturbing factor because they increase the mutation rate.

Table III, which is extracted from a paper by Stanford and Vance (1955), shows how examinations involving the

TABLE III.
Gonad Dose in mr.
(*After* Stanford and Vance, 1955.)

Region and Type of Examination.	Number of Films.	Male.	Female.
Skull	4	0·2	0·05
Chest	1	0·36	0·07
Foot	2	0·62	0·012
Barium meal	—	20·0	9·0
Abdomen (pregnant) ..	1	—	260·0
Lumbo-sacral junction (lateral)	1	15·0	800·0
Pelvis (antero-posterior) ..	1	1100·0	210·0

lower part of the abdomen and pelvic region greatly increase the dose to the gonads. Table IV expresses the same thing differently, and demonstrates forcibly how the relatively few examinations of the pelvic region are responsible for over half the gonad dose. Particular care must therefore be exercised in ordering examinations of this region in children and those of reproductive age, and of course during pregnancy.

TABLE IV.
Gonad Dose and Examinations.

Region.	Percentage of Total Examinations.	Percentage of Dose to Gonads.
Skull, chest, extremities	80	1
Pelvic region	3	65

Hopeful Future.

What of the future? In view of our incomplete knowledge of the effect, it is the duty of all of us to reduce the use of radiation to the minimum consistent with accurate and efficient diagnosis. The clinician can help by a more critical requesting of X-ray examinations, having a clear idea in his own mind of what he is asking for, and what he hopes to find or exclude, for a negative report can be as valuable as a positive one.

The radiologist, and those working with him, can do much to reduce radiation by the use of up-to-date techniques and materials. Efficient cones and shutters should be used to limit the X-ray beam to the part of the body under investigation, and it has been shown by direct measurement that a small reduction in the size of the beam will cause a substantial reduction in the dose scattered to more remote areas of the body. Over the years, the speed of X-ray screens and films has been increased, so that the film we now use is 40 times faster than the original glass photographic plates, with a consequent reduction in the amount of radiation required. The insertion of aluminum filters in the X-ray beam removes the softer rays, which are of no value diagnostically. There has been a tendency over the years, as better X-ray tubes and generators have become available, to use a higher kilovoltage or more penetrating X rays, which again has reduced the dose necessary. Many technical tricks have been introduced, such as simultaneous multiplane tomograms, in attempts to reduce the dosage. There is, of course, a constant search for improved contrast media, and recently experiments have been conducted with chelating agents and lead; lead would be an ideal contrast substance if only it could be introduced into and excreted from the body in a non-toxic form. Work is actively going on to try to discover a chemical means of protecting the living organism against the effects of radiation. This is still in its infancy, but it is already known that substances such as cysteine and glutathione do provide some protection, and it does not seem impossible to me that one day our patients will take a protective pill before their barium meal X-ray or microradiographic chest examinations. Perhaps the greatest single advance in recent years has been the introduction of the image intensifier, a device for amplifying a fluorescent image produced by X rays. When fully perfected, it will enable a great reduction to be achieved in the amount of radiation necessary for screening, and it has made clinical cineradiography practicable, thereby enabling us to extend our investigations in many regions such as the œsophagus and urinary tract. The following will give you some idea of what has been done: actual measurements show that the skin dose for one film of the abdomen has been reduced to one one-hundredth in 15 years in the Nuffield Institute—from 1·4*r* in 1938 to 0·13*r* in 1952 to 0·012*r* in 1953 (using the image intensifier).

It will be seen that protection from the harmful effects of radiation is not a new problem, but one which has been receiving attention almost since the day Röntgen discovered X rays. Much has already been achieved. In diagnostic radiology, epilation and X-ray dermatitis have been eliminated, and I hope I have convinced you that the leukæmogenic effect is negligible. Much attention is at present being directed towards methods of minimizing the genetic hazard. It seems to me that there is no danger to patients over the age of 40 years subjected to investigation by diagnostic X rays when performed by trained radiologists using modern apparatus, and I think this should be made plain to the public. With patients still likely to have children, greater care must be exercised, not because of any danger to the patients themselves, but because of the unknown risk of increasing the mutation rate. The clinician should think twice before ordering X-ray examinations of the pelvic region in children and young adults.

Conclusion.

I would like to quote a few sentences from a recent editorial of the *American Journal of Roentgenology*:

> Consider the most beneficial use of radiation that we can think of—the diagnosis and treatment of disease. No one can question the enormously important benefits that radiation offers in improving our health. To deny ourselves this tool is to take a step back toward the dark ages. Yet, as we now know, it carries some element of risk, not necessarily to ourselves but to some unknown, unborn person at some unknown time in the future. How can we balance the choice between our own health—or possibly even our own survival—between this and that unidentifiable life of the future. I suspect the answer is clear, but can we be sure?
>
> For the present, we must preserve our sense of proportion. Through misunderstanding and many confusing public statements, the public does not know what to do. This is becoming more evident daily, as we hear of people refusing to have chest roentgenography or dental examinations. There is no future for that unborn child if first we die of tuberculosis or infection. Here is where our sense of proportion enters.

Summary.

The history of the development of medical radiology and of its hazards is briefly reviewed.

The risk of diagnostic radiology producing malignant diseases in adults and fœtuses is shown to be negligible.

The possible serious genetic effects of irradiation of the gonads in those capable of reproduction is demonstrated.

Some advances minimizing radiation hazards are listed, and a plea is made to inform the public that diagnostic radiology is relatively innocuous.

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ACUTE OTITIS MEDIA IN CHILDREN: A SURVEY.

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LATE in 1956 it seemed that the time was opportune to consider the forms in which acute otitis media presented in an unselected group of children with acute symptoms relating to the ear. Having had personal experience of a comparable group in pre-antibiotic days, during which streptococci of various types predominated bacteriologically, and having watched the decline of the streptococcus and the virtual disappearance of scarlet fever as an endemic disease, we shall try to answer the question which has arisen as to what effect these changes have had on the various types of otitis media. Do the old lines of treatment still have any value or are they ruthlessly to be supplanted?

An investigation was undertaken of patients presenting with ear disease in the casualty rooms of the Royal Alexandra Hospital for Children, Sydney, in order to encourage more respect for the value of careful diagnosis, to establish the necessity or otherwise for wholesale exhibition of penicillin or other antibiotics, and to seek a better balanced approach to the disease. Accordingly, instructions were issued for the guidance of casualty officers and the registrars at the out-patient department. With the help of visiting ear, nose and throat surgeons, the registrars carried out painstaking observations along the lines indicated in the following.

1. All patients suffering from aural pathological conditions or symptoms were to be referred to the out-patient registrar within 24 hours or, after the week-end, before 2 p.m. on Monday.

2. Treatment given was to be limited to: (*a*) Treatment of the cause in the nose and throat, by (i) nasal drops, e.g. "Argyrol" (5% or 10%) (no vasoconstrictors); (ii) inhalations if the child was old enough. (*b*) Local: if otorrhœa was present, simple cleansing of the meatus was to be performed. (*c*) For the relief of pain and sleeplessness: *Pulvis Ipecacuanhæ Composita*, or *Haustus Chloralis*, or A.P.C. mixture for older children.

3. Antibiotics were to be given only if the temperature was above 102° F. Penicillin V ("Distaquaine") tablets were to be given by mouth, initially 400,000 units, then 200,000 units every six hours, sufficient being supplied to last until the patient's visit to the out-patient department.

4. A chit notifying treatment was to be sent to the out-patient department.

5. No pathological tests were to be done on aural discharges at this stage. For better understanding of the rationale of the approach, the following guide, in the form of a classification of otitis media, with an attempted indication of the pathological patterns and consequent variations in treatment, was given to the registrars.

Classification of Otitis Media.

Otitis media can be classified into three groups: A, acute, non-suppurative; B, acute, suppurative, with or without otorrhœa; C, recurrent or acute or chronic suppurative.

Group A: Non-suppurative otitis media is due to nasal or throat infections. The mechanism is blockage in the Eustachian tubes. The cause should be treated in accordance with the Casualty Department schedule, and no medication should be given to the ear. If the condition is subsiding, treatment is continued; if the symptoms persist, it has probably progressed to group B.

Group B: In acute catarrhal or suppurative otitis media, if the pain increases, myringotomy may be necessary. If the temperature rises with an increase in pain, myringotomy and a determination of bacteriological organisms and sensitivity should be performed; antibiotics should be given if the condition is very toxic. The following are important: sleeplessness, the state of the tongue and the general appearance. The indications for myringotomy are a bulging drum, increasing pain and increasing inability to sleep.

Group C: In cases in which otorrhœa persists for over four weeks or has been recurrent, patients should be referred to the ear, nose and throat surgeon.

In a period of twelve months 351 patients were studied and useful results were obtained despite difficulties in recording and tracing patients, caused largely by the social status of the population involved. Generally speaking, the investigation justified the belief that, despite the change in bacterial flora, primarily acute middle ear disease in children under the age of eight years is due to Eustachian tube blockage or to catarrh, and treatment is from the outset that of the upper part of the respiratory tract, notably of the post-nasal space.

Accurate classification presented difficulties consequent on the merging of one aspect of the disease into another. Apparent inconsistencies are inherent in the nature of the condition, as previous history and the state of the rest of the upper part of the respiratory tract must be taken into account.

The 351 patients in the survey treated at the Royal Alexandra Hospital for Children during 1957 were classified as follows: acute and recurrent Eustachian tube obstruction, 111 patients; acute catarrhal otitis media, 116 patients; recurrent catarrhal otitis media, 45 patients; acute suppurative otitis media, 59 patients. There was also a group of 25 patients with acute or chronic mastoiditis, with or without complications, who were treated in the same period.

One of the aims of this study was to clarify the diagnostic classification of middle ear disease in young children. The greatest difficulty lay in determining when Eustachian tube obstruction was complicated by Eustachian tube or middle-ear catarrh, and at what stage catarrh could be regarded as having developed into suppurative otitis media. Otorrhœa, if watery, was still regarded as a manifestation of catarrhal inflammation. All cases in which pathogens were cultured or in which physical signs and discharge were consistent with a presumption of bacterial invasion of the middle ear were classed as suppurative otitis media. Into the catarrhal group, acute or recurrent, came 43% of all the patients seen. The clinical

picture was often coloured by the primary disease of the upper part of the respiratory tract.

The group of 59 cases classed as acute suppurative otitis media could have been numerically enlarged had all cases of otorrhœa been included. Those patients with a watery discharge were put into the catarrhal group. Bacteriological culture and sensitivity tests were available for few patients save those undergoing myringotomy. Included were *Staphylococcus albus*, *Hæmophilus*, diphtheroids, *Bacillus coli communis* and hæmolytic streptococcus, usually in conjunction with another organism. The numbers were too small to be of any significance, but suggested that today *Streptococcus pneumoniæ*, *Staph. aureus*, and *Hæmophilus* are most to be respected.

The factors of which special note was made were age, previous ear disease, past acute infectious fevers, experience of antibiotic therapy for this or other disease, bacteriological features of the present ear disease and sensitivity to antibiotics when material was available, and the effectiveness of treatment immediate or remote.

Age Distribution.

As regards age distribution, the youngest patient in the series was four weeks old, the oldest 12 years, with the highest incidence between nine months and five years, the maximum being in the region of two years.

Previous Aural Pathological Conditions.

Of the total 351 patients who presented at this hospital for the first time during this survey, 158 had had previous ear trouble. The largest proportion of these, numbering 45, was classed as suffering from recurrent catarrhal otitis media. A few had a florid suppurative otitis media, and the remainder Eustachian tube catarrh or obstruction secondary to a nasopharyngeal infection.

Acute Infectious Disease.

None of our cases was associated with a specific acute infectious fever. Patients were questioned regarding previous experienec of this nature, with particular reference to measles and pertussis. In most cases the children who had had pertussis had also suffered from measles. Of six children who had been treated for meningitis previously, two had had meningococcal septicæmia treated within the previous few months with penicillin and sulphonamides; in one case the meningeal infection was influenzal, probably of otitic origin, though the patient had had much antibiotic treatment for otitis media and had had pneumonia; in another, pneumococcal infection was associated with otitis media, for which penicillin and sulphonamides had been successfully given. Thus the following information of previous relevant acute infectious disease was obtained: 111 patients had had measles, 27 pertussis, six meningitis and three scarlet fever.

Duration of Symptoms and Signs.

Duration of symptoms and signs varied according to their nature, with no one predominating. Along with symptoms referable to the upper part of the respiratory tract came vomiting, which was more frequent than expected, and convulsions, which claimed prior interest in some ten cases. Earache, pulling at the ears and otorrhœa gave the usual indication of the site of the disease, the usual onset being 24 to 48 hours before advice was sought, but there was also a group of patients who had suffered persistent pain for many days whilst under antibiotic therapy. Measures to relieve post-nasal congestion effectively put an end to their distress.

Physical Findings.

As one would expect, physical findings in the ear varied from slight infection and retraction of the drum to gross infection and bulging, spontaneous watery otorrhœa, purulent discharge and in one case the bullous inflammation classified as myringitis bullosa. The clinical condition of the patient did not necessarily correspond with the appearance of the tympanic membrane. In some cases in which no other cause apart from otitis media was found, the child appeared very ill, although there was only a mild inflammation of the drum. In others the drum was very inflamed, but the child appeared well. The time taken for the appearance of the drum to approach normality did not appear to be shortened by the exhibition of antibiotics used in conjunction with a post-nasal toilet as compared with the latter alone. The drum which had been treated with ear drops was difficult to assess clinically, and was usually still painful. The medication seemed at times distinctly irritative, causing a chemical otitis externa, which obscured the landmarks.

Treatment.

In pursuance of the policy of this project, all patients received treatment to their nasopharynx along the lines indicated. In the 73·2% of cases regarded as belonging to the Eustachian tube blockage group, the only addition was penicillin given orally in those cases in which disease of the upper part of the respiratory tract was considered to be the primary illness. As ear disease seldom of itself causes pyrexia over 102° F., it seemed reasonable to assume that a patient with a temperature higher than this would need treatment for the upper part of his respiratory tract, and antibiotics were exhibited.

Progress of the purely obstructive to the catarrhal stage was negligible in those who were traceable. Naturally, a number of these would not seek further help after drainage was reestablished and failed to report. In any cases in which concern was felt, the almoner contacted the homes, usually to find that no further attendance was necessary. Again, penicillin was used if necessary for the primary disease, with a recurrence rate of 7% in the 43 cases so treated as compared with 4% in the 73 cases in which antibiotics were not thought necessary.

Of the patients with recurrent catarrhal otitis media, after initial relief of symptoms 34 were subsequently subjected to surgery, whereas only six of those in the acute group are so far known to have needed such procedures.

Bulging Tympanic Membrane and Myringotomy.

Before speaking of those patients classed as suffering from acute suppurative otitis media, it is necessary to consider the subject of the bulging tympanic membrane, and the indications for and present status of the operation of myringotomy. Indications for incision were noted in the advice given for the care of these patients in the initial instructions, but the conditions under which the work was carried out demanded very nice judgement in assessing the significance of the bulging drum and its relationship to treatment. It is to the credit of those who were handling these patients that, with restricted use of antibiotics, in only one case did otorrhœa occur spontaneously. In that case the organism was penicillin resistant. In one other, fullness of the drum recurred, myringotomy was then performed, and a diphtheroid organism was cultured. In the cases in which myringotomy was performed, interference was justified by the operative release of fluid or pus and the relief of symptoms.

Treatment employed in the presence of a bulging tympanic membrane was as follows: conservative, i.e. nasal toilet, 23 cases; conservative *plus* myringotomy, five cases; conservative *plus* antibiotics, 17 cases; conservative *plus* myringotomy and antibiotics, eight cases. Treatment and classification corresponded. The conservatively treated group usually could be classed as suffering from catarrhal otitis media.

All those patients in whom myringotomy was performed were classed as having acute suppurative otitis media as the exudate grew an organism. However, these patients fell into two distinct groups. (i) Those from whom the following organisms were cultured and for whom antibiotics were not considered indicated: diphtheroids, three patients; *Str. viridans*, one patient; *Staph. albus*, one patient. (ii) Those from whom the following organisms were cultured and for whom antibiotics were used: pneumococci, three patients; *Staph. albus*, four patients; hæmolytic streptococcus, one patient. In this latter group

patients were treated with antibiotics according to clinical judgement and the recommendations laid down for this trial. They exhibited a greater degree of toxicity and progressive symptoms compared with the former class. Thirteen patients underwent myringotomy. The numbers are small but representative, and indicate the useful role still left to the procedure in relief of tension of the middle ear.

Apart from patients undergoing myringotomy, otorrhœa of recent origin was noted by the parents in 83 cases. A diagnosis of acute suppurative otitis media was made in 59 cases, including those in which myringotomy was performed.

Complications.

In all groups treated there were 11 children who had relapses, seven of whom had had previous ear disease. Eight of these 11 children had had penicillin on previous occasions, four had had it on this occasion, and one had not had any. All were eventually referred for surgery of the ear, nose and throat.

Two patients were subjected to cortical mastoidectomy. One had had no previous ear disease, was treated with penicillin, and after four weeks of conservative treatment was justifiably subjected to operation. The organism cultured from the mastoid wound was *Staph. aureus*, sensitive to penicillin. The other patient had had a previous cortical mastoidectomy (no growth had been obtained on culture) performed on the other ear, and she had failed to report for follow-up treatment. The organism was a pneumococcus in a subperiosteal abscess.

Previous Exhibition of Antibiotics.

In an effort to assess the effect on the upper part of the respiratory tract and on ear infections of the previous exhibition of antibiotics to the patient in question, inquiry regarding previous treatment along these lines revealed that 202 (57%) of the 351 patients had been so treated with the following distribution: penicillin alone, 86 patients; penicillin and sulphonamide, 56 patients; sulphonamides, 26 patients; other antibiotics, with or without penicillin, 39 patients.

Antibiotics, and for simplicity the sulphonamide group will be included under this term, had been administered previously for various reasons to 202 children. In the majority of cases the drug was penicillin, and its exhibition closely paralleled the number who gave a history of having suffered from measles, but no inquiry was made as to whether the treatment was related to that disease. Known sensitivity to penicillin was noted in a few cases. There was little evidence of the use of broad-spectrum antibiotics. Sulphonamides with or without penicillin had been taken by 82 patients, a combination of both by 56, or 39%, of the penicillin-treated group. No conclusions about the effect on the bacterial flora could be reached owing to lack of information concerning time relationships. It certainly would not seem to have had any permanent effect in eliminating organisms pathogenic in the nasopharynx.

The Place of Mastoidectomy.

This conclusion was underlined by observation on patients coming to mastoidectomy during the same period, and a consideration of some aspects of this disease is necessary, especially in regard to numerical incidence in the pre-antibiotic era and at present, and also in regard to bacteriology (Table I).

The yearly totals of mastoidectomies performed during the 20 years from 1938 to 1958 reveal a numerical steadying after the peak years of the 1940's, when measles were epidemic and the hæmolytic streptococcus was endemic.

In 1957, on patients admitted to the public wards of the Royal Alexandra Hospital for Children, 33 mastoidectomies were performed, 14 for disease of very recent onset presenting with the classical post-auricular subperiosteal abscess. Analysis reveals an interesting relationship between the previous experience of these subjects with regard to treatment with antibiotics and the exhibition of antibiotics in the present illness. Only two had escaped, one from a remote farm and the other from a family who do not speak English. In at least 60% of cases the subperiosteal abscess developed during antibiotic therapy. One patient had had his recurrent post-auricular swelling reduced by three antibiotics in turn, when at last on the fourth occasion his attendant, frustrated by the lurking *Hæmophilus*, referred him for treatment in hospital. The organism was sensitive to all the drugs used, but they could not be envisaged as reaching the germs enmeshed in the organized pultaceous material with which the mastoid structure had been replaced. Table II presents an analysis of these cases.

TABLE I.

The Number of Mastoidectomies Performed in the Period 1938 to 1958.

Year.	Number of Mastoidectomies.
1937–1938	48
1938–1939	45
1939–1940	46
1940–1941	59
1941–1942	51
1942–1943	101
1943–1944	103
1944–1945	91
1945–1946	51
1946–1947	30
1947–1948	31
1948–1949	55
1949–1950	65
1950–1951	34
1951–1952	32
1952–1953	28
1953–1954	10 simple. 16 modified radical.
1954–1955	25 simple. 2 modified radical.
1955–1956	20 simple. 5 modified radical.
1956–1957	20 simple. 4 modified radical.
1957–1958	25 simple. 3 modified radical.

In the cases of recent onset, *Str. pneumoniæ* was present in six, *H. influenzæ* in four (also in combination with *Str. pneumoniæ* in one case, with *Staph. aureus* in another), hæmolytic streptococcus in two cases, *Staph. aureus* alone in one, combined in one.

These findings contrasted with those for swabs taken at operation in the group with chronic conditions; these swabs yielded *Staph. aureus* in five cases, *Str. pneumoniæ* in two, *B. coli communis* in three, hæmolytic streptococcus in two, *Staph. albus* in one. An *Hæmophilus* was present with the *Staph. aureus* in one baby.

Penicillin sensitivity of the organism was usual even with the staphylococci. Though appropriate antibiotics had been exhibited in most cases at some time during the course of the disease, the persistence of the infection indicated that organisms in the periphery of the mastoid process are inaccessible to the available concentrations of the drugs. One patient developed a classical extradural abscess tracking down to his jugular foramen after having numerous courses of penicillin with a sensitive *Staph. aureus*.

Acting empirically, all patients operated on by one of us (P.R.D.), whether they had acute or chronic disease, had "Chloromycetin" powder blown into their operation wound, which was then closed over a glass drain. Healing was by first intention in all cases but one, in which the wound gaped. Antibiotics were not used by any other route save in the patient with the extensive extradural abscess who appeared mortally ill but recovered dramatically after operation.

Functional Result.

The final test of all treatment of ear disease, the functional result of the ear now rendered dry and the drum restored, is the ability of the patient to hear. Results

Table II.
Analysis of Cases of Mastoidectomy.

Case.	Age.	Onset.	Duration of Symptoms.	Previous Antibiotics.	Organism.	Sensitivity.
1	6 months.	Earache, post-auricular swelling 7 days before. Recurrence.	10 days. 1 day.	Penicillin at outset.	*Strep. pneumoniæ.*	Sensitive to all antibiotics.
2	4 years.	Aural discharge, post-auricular swelling.	4 weeks.	Penicillin, "Chloromycetin".	*H. influenzæ, Staph. aureus.*	Penicillin insensitive.
3	9 months.	Post-auricular swelling.	2 days.	Penicillin in the present illness.	*Strep. pneumoniæ, H. influenzæ.*	Sensitive to all antibiotics.
4	5 years 3 months.	Recurrent pain and recurrent post-auricular swelling.	3 months.	Penicillin and broad-spectrum antibiotic sulphadiazine.	*Hæmophilus.*	Sensitive to all antibiotics.
5	3 years.	Otorrhœa.	4 weeks.	Nil.	No growth—later *Staph. aureus.*	Sensitive to all antibiotics.
6	6 months, 8 months, 12 months.	Right facial paralysis, left post-auricular swelling, recurrence in wound on the left.	2 days.	? Penicillin after left mastoidectomy.	No growth, *Strep. pneumoniæ.*	Sensitive.
7	9 months.	Pre-auricular swelling.	4 days.	Penicillin in present illness.	*Strep. pneumoniæ.*	Sensitive to all antibiotics.
8	4 years.	Post-auricular swelling.	2 days.	?	Hæmolytic streptococcus.	Sensitive to all antibiotics.
9	12 months.	Post-auricular swelling.	24 hours.	Sulphonamides.	Hæmolytic streptococcus.	Sensitive to all antibiotics.
10	12 months.	Otorrhœa, post-auricular swelling.	1 week 1 day.	Sulphadiazine.	*Strep. pneumoniæ.*	Sensitive to all antibiotics.
11	11 months.	Post-auricular swelling.	24 hours.	Nil.	*Strep. pneumoniæ.*	Sensitive to all antibiotics.
12	2 years 5 months.	Otorrhœa, recurrent post-auricular swelling.	3 weeks.	Penicillin at onset.	*Staph. aureus.*	Insensitive to penicillin.
13	21 months.	Otorrhœa.	20 months.	Penicillin at onset.	*B. coli communis, B. proteus.*	*B. proteus*, sensitive to "Chloromycetin".
14	11 years.	Otorrhœa.	Several years.	Unknown.	*B. coli communis, B. pyocyaneus.*	Penicillin-insensitive.
15	9 years.	Otorrhœa.	8 years 5 months.	?	*Staph. aureus.*	Sensitive to all antibiotics.
16	6 years.	Otorrhœa with acute exacerbation.	3 years.	——	*Staph. aureus, B. coli.*	Penicillin-sensitive, penicillin-insensitive.
17	9 years.	Chronic otorrhœa, cerebral irritation.	Years, 24 hours.	Penicillin frequently.	*Staph. aureus.*	Sensitive to all antibiotics.
18	5 months.	Recurrent otorrhœa.	4 months.	——	*Staph. aureus, Hæmophilus.*	Penicillin-insensitive.
19	9 years 6 months.	Chronic otorrhœa.	——	——	*B. coli.*	Penicillin-insensitive.
20	8 years.	Recurrent otorrhœa.	4 to 5 years.	——	*Staph. albus.*	Insensitive to penicillin.

on a useful scale will not be available from this survey for several years. It would be too laborious to try to assess such a large group by anything but pure tone audiometry. A recent survey of treatment of otitis media in general practice in Britain showed a rate of hearing loss of 4%. We have no reliable figures of incidence of loss in this country for comparison.

The survey supported the need for correct evaluation of the patient and his ear condition before instituting therapy, the importance of recognition of the basic pathological importance of the nasopharynx in treatment, the lack of wisdom in overtreating a patient for a degree of pathological change which has not occurred, the unreliability of the antibiotics once the infection has invaded the recesses of the middle ear and mastoid process, and the satisfactory and rapid relief afforded by judicious surgical intervention enabling natural forces of repair to come into play in the wake of adequate drainage. The lines of treatment carried out appeared to be justified by the small recurrence rate and by a gratifyingly small incidence of complications.

Summary.

A survey was undertaken to try to establish criteria of classification of acute ear disease in children and to determine the nature of the bacterial flora at present affecting the Eustachian tube and middle ear.

Treatment was restricted to post-nasal toilet, antibiotics if the temperature was over 102° F., and myringotomy where necessary. Relapses and complications were few.

A review of the mastoidectomies performed during the same period demonstrates the identical tendencies to a change of bacterial invaders and a failure of antibiotics given parenterally to eliminate the established organisms.

Reviews.

Where Love Is: The Fostering of Young Children. By Josephine Balls, with preface by John Bowlby, M.D.; 1958. London: Victor Gollancz, Limited. 7½" x 5", pp. 224. Price: 22s. 6d.

Miss Josephine Balls is a child welfare officer in the service of the Northumberland County Council; from her experience there and in a child guidance clinic she has written an appealing, understanding book of case records of deprived children who have come under the care of the local authority.

The title of her book is taken from the Book of Proverbs —"Better a dinner of herbs where love is, than a stalled ox and hatred therewith"—and the dedication is to "The Foster Families of Northumberland". Miss Balls sets out to show some of the problems and the successes of the change in system of child care, which meant the closing of institutions and the placing of children in foster homes.

Dr. Bowlby, in the preface, states that "crippling and stunting of personality is still with us. Many children grow up to be social misfits unable to be happy themselves and unable to give happiness to others". Many of the delinquents and social misfits come from this group of deprived children, and nearly all come from homes where love has not been the practice. Many of the children coming under the care of the local authority have been neglected and badly mismanaged, many have permanently damaged personalities, so that the task of placing them in suitable private homes is not easy. Love is not a very potent force in many of the foster homes, and the task of the child welfare officer in selecting homes is not easy.

Miss Balls describes her protégés and their foster parents in easy, fluent language. Patrick for instance was "a jewel worthy of a better setting"; Michael "chopped up anything that was handy, including clothing, his own hair and the cat's whiskers".

Anyone interested in people will enjoy this book and gain from reading it; it is not technical and is thoroughly readable. However, its main value will be for social workers and nurses, particularly baby health centre sisters, and it should find its way into libraries of hospitals and into the book boxes of child study classes, so that parents, too, can gain better understanding of families and of some of the causes and results of family breakdowns.

Fractures and Dislocations. By George Perkins, M.C., M.Ch., F.R.C.S.; 1958. London: The Athlone Press. 9½" × 6", pp. 372, with 225 illustrations. Price: 57s. 6d. (English).

PROFESSOR PERKINS is well known as a teacher as well as for his unorthodox views on fracture treatment. His latest publication proves to be no disappointment in either regard; however, it is a curious mixture of sound common sense on the one hand and dubious and even dangerous counsel on the other. The dominant theme of treatment by exercise is founded on the belief that rest is synonymous with stiffness—a belief that most would regard as untrue. Thus violation of most established principles is apparent on every page, and even as the first principle in the treatment of wound healing rest is sacrificed to early joint movement. Immobilization of dislocated joints after reduction is said to be unnecessary, although a concession is made in the case of the shoulder "to avoid being blamed for a recurrence". Recurrence is said to be common. A man is illustrated standing with his leg unprotected 14 days after Küntscher nail fixation of his femur. This is certainly spectacular, but is it desirable?

In discussing the treatment of non-union, Professor Perkins states his belief that it is necessary only to freshen the bone ends and then to treat the condition as a recent fracture. Perhaps this is the most surprising statement in a book full of surprises. There is no mention of the valuable contributions of Phemister in this regard, or of the proven value of intramedullary fixation.

These are but a few of many statements which orthopædic surgeons will find impossible to reconcile with their own experience.

The book is profusely illustrated with excellent radiographs, and the easy style makes interesting reading. It is really suitable only for those of mature experience in the treatment of injuries.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Contributions of the Physical, Biological and Psychological Sciences in Human Disability", by Renato Contini, Sidney Fishman *et alii*; "Annals of the New York Academy of Sciences", Volume 74, Art. 1; 1958. New York: The New York Academy of Sciences. 9" × 6", pp. 160, with many illustrations. Price: $3.50.

Papers from a conference held in February, 1958.

"Surgery of the Sympathetic Nervous System", by Professor Sir James Paterson Ross, K.C.V.O., LL.D., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S.; Third Edition; 1958. London: Baillière, Tindall and Cox. 9" × 6", pp. 182, with 51 illustrations. Price: 35s. (English).

This book, from the Surgical Professorial Unit of St. Bartholomew's Hospital, has been largely rewritten since the previous edition was published.

"Congenital Atresia of the Small Intestine: A Roentgenographic Study of 24 Cases", by H. Gladnikoff, *Acta Radiologica*, Supplement 164; 1958. 9½" × 7", pp. 58, with 19 illustrations and one table. Price: Sw. Kr. 25.

From the Roentgen Department, Sachska Barnsjukhuset, Stockholm.

"Studies on the Effect of Thyrotropic Hormone on the Thyroid Function in Man", by Jerzy Einhorn, *Acta Radiologica*, Supplement 160; 1958. 9½" × 7", pp. 107, with 23 illustrations and 22 tables. Price: Sw. Kr. 30.

From Radiumhemmet, Karolinska Sjukhuset, Stockholm.

"Coarctation of the Aorta: Aortographic Studies Before and After Operation", by Bror Brodén and Johan Karnell, *Acta Radiologica*, Supplement 165; 1958. 9½" × 7", pp. 61, with 37 illustrations and four tables. Price: Sw. Kr. 30.

The title is self-explanatory. The work comes from Roentgen Department I and the Heart Clinic, Södersjukhuset, Stockholm.

"Nephrographic Effect and Renal Arteriographic Damage: An Experimental Study", by Carl-Gustaf Helander, *Acta Radiologica*, Supplement 163; 1958. 9½" × 7", pp. 87, with 20 illustrations and 14 tables. Price: Sw. Kr. 30.

A survey and discussion of a collected series of papers on original investigations.

"The Vascular Anatomy of Long Bones: A Radiological and Histological Study", by Gunnar Tilling, *Acta Radiologica*, Supplement 161; 1958. 9½" × 7", pp. 107, with 47 illustrations. Price: Sw. Kr. 25.

The author has been particularly concerned with the growing period.

"Anatomy for Surgeons: Volume 3, The Back and Limbs", by W. Henry Hollinshead, Ph.D.; 1958. New York: A Hoeber-Harper Book. 10½" × 7", pp. 920, with 785 illustrations. Price: $23.50.

The author is Professor of Anatomy, Mayo Foundation, University of Minnesota.

"Polysaccharides in Biology: Transactions of the Third Conference, May 29, 30 and 31, 1957, Princeton, N.J.", edited by Georg F. Springer, M.D.; 1958. New York: The Josiah Macy, Jr. Foundation. 9" × 6", pp. 254, with many illustrations. Price: $4.75.

Contains papers and discussions on two subjects: homopolysaccharides, and nucleotides and saccharide synthesis.

"The Chemical Prevention of Cardiac Necroses", by Hans Selye, M.D., Ph.D., D.Sc.; 1958. New York: The Ronald Press Company. 9" × 5⅞", pp. 246, with 20 illustrations and 15 tables. Price: $7.50.

The author's own experimental work is coordinated with related observations in the world literature.

"Enzymes in Blood", by L. P. White *et alii*; "Annals of the New York Academy of Sciences", Volume 75, Art. 1; 1958. New York: The New York Academy of Sciences. 9" × 6", pp. 384, with many illustrations. Price: $5.00.

Papers from a conference held in February, 1958.

"The Basic and Clinical Research of the New Antibiotic, Kanamycin", by Maxwell Finland, R. B. Aronsohn *et alii*; "Annals of the New York Academy of Sciences", Volume 76, Art. 2; 1958. New York: The New York Academy of Sciences. 9" × 6", pp. 390, with many illustrations. Price: $5.00.

Papers from a conference held in July, 1958.

"Surgical Convalescence", by F. Curtis Dohan, N. Henry Mass *et alii*; "Annals of the New York Academy of Sciences", Volume 73, Art. 2; 1958. New York: The New York Academy of Sciences. 9" × 6", pp. 58, with many illustrations. Price: $4.00.

Papers from a conference held in 1958.

"A Doctor in Korea: The Story of Charles McLaren, M.D.", by Esmond W. New; foreword by the Reverend George Anderson; 1958. Sydney: The Australian Presbyterian Board of Missions. 8½" × 5½", pp. 58, with many illustrations. Price: 10s. 6d.

The story of a man of faith.

The Medical Journal of Australia

SATURDAY, FEBRUARY 28, 1959.

WORK FOR THE HANDICAPPED.

It is over a decade since an organized rehabilitation service was inaugurated by the Commonwealth for certain groups of beneficiaries. Since then a certain amount has been done and a great deal has been said, but the subject needs constant review. In the years 1944-1945 and 1946-1948 some experience was gained in the reestablishment of ex-servicemen, but by 1948 two problems had become apparent—the assessment of individuals as being suitable for rehabilitation and the selective placement of handicapped persons. The assessment of an individual is an extremely complex task. It involves the taking of a careful history commencing with the family background and progressing through schooling to the industrial background. Then the assessment of the physical handicap occupies much thought, especially in relation to whether improvement is likely to occur or whether treatment is likely to interfere with continued employment. In other words, a careful assessment of the "whole" individual has to be made. If the assessment suggests that the individual is worthy of help, it seems fundamental that there should be some reasonable chance of finding suitable employment. This factor has been successfully glossed over during the period of expanding economy, but, with the alteration in chances of employment which are apparent, it seems deceitful to offer treatment to make employment possible and after a somewhat lengthy period to announce that there are no jobs available. Unfortunately, up to this stage, another important aspect in rehabilitation has not been dealt with by the authorities—i.e., the provision of sheltered workshops. These sheltered workshops remain an excellent method of being sure that an individual is sincere in desiring employment; if observation in a workshop establishes his worth, a prospective employer can be approached with much more assurance.

It can be reiterated that selection and assessment of those requiring rehabilitation are a long and exacting process, and those qualified to make assessment are medical practitioners—not necessarily specialists, who may be enthusiastic about methods of treatment and not about reestablishment, and not necessarily physical medicine specialists, who may be wedded to physical methods. The ancillary services can be of immense help, but the decision rests with the doctor. He has the responsibility of deciding to use limited community resources in an attempt to help.

Since 1948 there have been many State, Federal and international conferences on rehabilitation. Many excellent papers have been read and discussed. But have we, as Australians, done very much to see that handicapped people, worthy of being assisted, have a reasonable chance of employment? Have we been prepared to forget our small sense of being important and sit around a table to discuss how we can get Bill Jones a job? The questions are important and demand answers. At times, it is felt that we have not progressed very far from the habits of primitive tribes who leave their unproductive and sick members to die. We put them on a pension, which may be less realistic than primitive man's idea and is certainly more lingering. We see hospitals establishing rehabilitation centres, and statutory bodies establishing new schemes to help their eligible subjects, and these have their place and value. However, we have also had to suffer the spectacle of a scramble to obtain the few jobs available in some States. As a result, unworthy persons have sometimes obtained employment, with consequent failure; this has been used to emphasize the necessity for a pension, but has also closed the opportunity with the employer concerned for another handicapped person to get a job.

If we, as a nation, believe in rehabilitation as much as we have talked about it in the past decade, it is time we sank our differences and had some round-table talks in each State to discuss the situation frankly. Perhaps then those in the community who could provide suitable employment would do so. It is certainly to be hoped that the Federal Council, which has made strong and sincere attempts to get some of the practical difficulties sorted out, will persist and not be discouraged.

THE SEARCH FOR NEWER AND BETTER STEROIDS.

While physiologists and biochemists have turned their attentions from the purely morphological effects of hormones towards the more fundamental actions of these substances, pharmacologists continually ask that chemists will, in defiance of nature, produce "freak" hormones which exploit one property of a hormone at the expense of others. These two groups of workers are not heading in opposite directions; they are working upon different planes or at different levels. Biochemists, for example, are pleased with their discovery that thyroxine promotes the uncoupling of some of the phosphorylations which occur during the oxidation of certain substances such as β-hydroxybutyrate. Again, the fundamental action of ACTH appears to consist of promoting the conversion of cholesterol to pregnenolone. Older books of physiology describe the action of testosterone in terms of the effects of castration and the repair of such changes following the administration of androgens. Today physiologists are more interested in answering the question of how these changes are brought about. What, for example, is the meaning of the decline in the alkaline and acid phosphatase content of the prostate and seminal vesicles following castration and their restoration by testosterone? Is the beneficial effect of testosterone upon spermatogenesis related to the fall in aconitase and fumarase content of the ventral part of the prostate following castration and the return to normal levels following the administration of testosterone?

In the case of corticosteroid hormones, various workers are looking for the fundamental site of action of hydrocortisone. It is generally held that the hormone affects the function of most of the cells of the body, but how

remains uncertain. Meanwhile pharmacologists have urged chemists to produce a steroid which suppresses the fundamental inflammatory reactions of the body without causing salt-retention, osteoporosis, diabetes, dyspepsia, virilization, hypertension, striæ or lowered resistance to infection. So far this tall order is a long way from being fulfilled. Certain steroids have such powerful anti-inflammatory properties that therapeutic doses do not cause diabetes, osteoporosis, salt-retention, hypertension, striæ or virilization. Nevertheless, the large doses required for diseases such as pemphigus and more resistant collagen diseases inevitably produce some or all of these undesirable effects. Moreover, dyspepsia with preparations for oral administration has so far defied the chemist and the pharmacologist alike. One of the most recent products designed to answer the requirements of the clinician for a safe, effective steroid is 9α-fluoro-16-methylprednisolone (dexamethasone). This hormone, discussed recently by P. F. Heffron, A. Vernet and J. D. N. Nabarro,[1] has greatly increased anti-inflammatory properties and is intensely protein-catabolic without causing salt-retention. The hormone promotes the excretion of potassium and increases the mobilization of calcium from bones and causes a rise in the fæcal excretion of calcium. These effects upon calcium metabolism seem to differ from those of other steroids so far studied and to contraindicate the use of dexamethasone in patients with hypercalcæmia—e.g., in those with carcinomatosis with osteolytic metastases in bone, sarcoidosis or vitamin D poisoning. On the other hand the adrenal-suppressing and diabetogenic actions of dexamethasone are of the same order as those of other steroids. It is made clear that it is too early to substantiate any claims of freedom from side effects.

The number of steroids available is now considerable, and new ones appear with bewildering frequency. The average practitioner, appreciating their complexity and their potency, but perhaps understanding little about them, is hard put to it to keep up with them. In this issue (see page 302) is the first of two articles on the steroids by Peter Hall in the "Brush Up Your Medicine" series. These are necessarily brief and condensed, but it is hoped that they will help the busy clinician to get his bearings. Meantime, we may care to meditate on the further example brought forward by Heffron, Vernet and Nabarro of the difficulty of splitting the desirable from the undesirable effects of steroids. Perhaps biochemists will soon be able to tell us how far these various properties are linked with the fundamental cellular or enzymatic actions of corticosteroids.

Current Comment.

WHO ACTIVITIES IN MEDICAL RESEARCH.

THE Executive Board of the World Health Organization has unanimously endorsed a programme for extended medical research, presented to it recently by the Director-General, Dr. M. G. Candau, that was characterized by several Board members as one of the most important steps in the Organization's history, opening up vast new horizons for international health action. The Director-General had drawn up the programme on the instructions of the Eleventh World Health Assembly, which met in Minneapolis, U.S.A., last year, when it was decided that further knowledge was needed on the causes, treatment and prevention of certain diseases common to mankind, as well as chronic diseases such as cancer and heart disease.

Describing the role of WHO in medical research, the Director-General observed that, great as any national research effort might be, there remained problems which could not be solved within the national boundaries of any one country. The clues to some of the greatest health problems of mankind might very well depend on their solution. Some required exploration in particular geographic areas, under particular climatic conditions, among populations of different races or in particular conditions of living. Coordinated research in different parts of the world which would yield comparable results, international teamwork which would pool talent, and better exchange of knowledge to expedite scientific progress must all become parts of the international endeavour if essential gaps in knowledge were to be filled.

The Director-General's report describes six categories of research problems particularly suitable for international collaboration. Chief among them are those of world-wide significance, such as the genetic description of population and the measuring of the incidence and prevalence of disease. Certain other problems, while not world wide, require study on a region-wide bases, like kwashiorkor and others common to all tropical countries. The second category includes communicable diseases: tuberculosis and many virus diseases that are universal, and malaria that requires a regional approach. Cancer, coronary thrombosis, hypertension, rheumatoid arthritis and diabetes mellitus represent a third category for which the comparison of health and illness in different environments and economic conditions may provide the key to understanding. The Director-General urged speedy exploration of these contrasts, which tend to disappear as a result of rapid social change and evolution. In describing the fourth category the report points out that an investigation of a rare condition often has had unexpected practical importance. For instance, an unusual kind of pulmonary hypertension has been reported in populations living above 4000 metres, the study of which might throw light on pulmonary hypertension in general. A fifth category arises from the need to assist highly skilled research workers to combine their experience for the expeditious solution of problems. Lastly, there is a need for international cooperation, because the necessary research resources are lacking in the countries where problems are found. Assistance from other nations, in either manpower or facilities or in both, is necessary, and could be arranged through an international organization like WHO.

At the conclusion of the discussions the Board requested the Director-General to continue the study and to submit his proposed research programme with budget estimates to the Twelfth World Health Assembly, which meets in Geneva in May.

IDIOPATHIC RETROPERITONEAL FIBROSIS.

A FEATURE common to many of the obscure conditions described during the past twenty years is that, once search is made for them, they are found to be much commoner, or at least less rare, than had been at first supposed. There are some indications that this may be so in the case of idiopathic retroperitoneal fibrosis (also referred to as non-specific periureteric fibrosis). Two cases recently described by Earle Hackett,[1] of Dublin, bring the total number of published cases, confirmed at autopsy or by operation, to only 22, most of them having been recorded in North America; however, one author collected seven cases in a few years at one centre in Britain.

The condition is of importance because it is a potentially lethal condition which can be relieved by timely surgical intervention, and of theoretical interest because of the difference of opinion as to its causation. The pathological

[1] *Lancet*, 1959, 1:173 (January 24).

[1] *Brit. J. Surg.*, 1958, 43:3 (July).

lesion consists of a dense retroperitoneal plaque of fibrous tissue, up to two centimetres in thickness, with very characteristic boundaries which correspond to the limits of the renal fascial compartments. Symptoms are produced by pressure on the structures which pass through this area. The ureters are the structures most commonly involved, and the condition was originally described as a type of urinary obstruction. In another paper in the same journal, J. C. Ross and L. F. Tinckler[1] describe a further case under the more generally used name of periureteric fibrosis. However, Hackett has no difficulty in showing that this name is misleading in that it restricts attention to one aspect of the condition. In one of his own cases, at autopsy a dense fibrous plaque was found, enclosing part of the right ureter, the aorta and inferior vena cava, and the para-aortic lymph nodes and nerve chains; most of the patient's symptoms had been due to urinary obstruction, but the aorta was narrowed and the inferior vena cava completely occluded. Hackett aptly remarks that the condition is one which "may present to the general practitioner as backache, intermittent claudication, or swelling of the lower limbs, to the urologist as anuria or oliguria with hydronephrosis, to the vascular surgeon as an aortic, caval or common iliac stricture, and to the pathologist as an unusual necropsy finding". In all accounts the Wassermann reaction has been consistently reported as negative, and the condition has been widely regarded as of inflammatory origin. On the other hand, Hackett presents cogent arguments against this view and, in spite of the absence of any history of trauma in all but a few instances, makes out a strong case for regarding the lesion as the end result of the organization of a hæmatoma or a fibrous effusion. In addition to the histological picture, this opinion is supported in one of his cases by the discovery of heavy deposits of hæmosiderin in the paraaortic lymph nodes. He also points out the marked similarity of the histological appearance in this condition and in pachymeningitis hæmorrhagica interna, in which this ætiology is acknowledged.

The treatment of the condition is surgical and consists of freeing the ureters from the fibrous tissue in which they are embedded. This is admirably described by Ross and Tinckler. Hackett mentions three cases in which treatment was by radiotherapy, but suggests that any benefit obtained was due to rest in bed. Cortisone is unlikely to be of any help in the primary treatment of the condition, but Ross and Tinckler suggest that it may be of assistance in suppressing the fibrotic reaction after operation; however, they accept the condition as being probably the outcome of an inflammatory reaction.

Whether or not his views are ultimately accepted, Hackett's able review of this condition is a useful contribution towards its proper understanding, and is likely to stimulate further interest. In his analysis of the reported cases he points out that many of them have been treated mainly from the urological viewpoint, and suggests that a degree of obstruction of the great vessels may have been overlooked in some. This leads him to suggest that in any case of unexplained ureteric block, it is worth comparing the brachial with the femoral pulse, and looking for engorgement in the superficial veins of the abdomen.

[1] *Brit. J. Surg.*, 1958, 43:58.

ANZAAS.

THE criticisms levelled at the Australian and New Zealand Association for the Advancement of Science by the President of the Adelaide Congress last year, Sir Marcus Oliphant, and by the Adelaide Press will be answered in the organization of the next congress, to be held in Perth from Monday, August 24, to Friday, August 28, 1959, according to the honorary local secretary, Professor D. E. White, of the University of Western Australia. Traditionally, ANZAAS congresses have been devoted to discussions, amongst scientists, of the most recent advances in their special fields, with a few public lectures in which eminent scientists have discussed recent scientific work for the benefit of the general public. The result has been a relative neglect of the stated aim of ANZAAS—to promote a spirit of cooperation between scientific workers and scholars and those in sympathy with science and scholarship generally. In releasing the first circular inviting membership for the congress this year, Professor White has indicated a number of ways in which the Perth congress will overcome this deficiency. Scientific lectures and discussions of current importance will be arranged for the man in the street. Some of these will be formal public lectures at 8 p.m., but it is also proposed to hold a series of informal lectures followed by discussions at about 5.15 p.m., in accordance with the example of the Adult Education Summer School. Daytime sessions will also be held for the general public, especially for teachers who will be on vacation during the congress. A young people's programme is being arranged, with the cooperation of the Education Department, and secondary school children with an interest in science—this should be all secondary school children—will be able to attend some of the specially designed talks to be given by eminent scientists. In addition to these programmes there will be specialist papers and discussions (sometimes in collaboration with specialist societies like the Australian Mathematical Society etc.) and symposia in which scientists specializing in diverse fields contribute to common problems.

Membership of the congress does not require any scientific qualifications and costs £2. Wives of members of congress and university, technical college and secondary school students may be admitted as associate members for £1. Members who wish to maintain an interest in the Association may pay an annual subscription of £2 2s. They then receive the *Australian Journal of Science* (published monthly). A subscription dating from July 1, 1959, is required to cover the Perth congress. Enrolment forms and further information may be obtained from the honorary local secretary, Professor J. R. A. McMillan, Science House, 157 Gloucester Street, Sydney.

SERUM LIPIDS IN HYPERTENSIVE PATIENTS.

ELIEL WARIS[1] has published an account of a study made in Finland in which a small battery of measurements—determinations of total lipids, cholesterol and phospholipid in serum, and electrophoretic separation of lipoproteins on paper with estimations of their amount—was made on 60 healthy persons and 101 hypertensives of both sexes. The introduction provides a comprehensive review of the literature on the interrelations between serum lipids, atherosclerosis and hypertension. The results, however, as commonly occurs in this confusing field of medicine, leave the reader rather bewildered. One has to struggle with differences due to sex and age trends, and to focus on to each of the various variables in turn, such as alpha lipoprotein, alpha lipoprotein cholesterol, alpha lipoprotein phospholipid, alpha lipoprotein P/C ratio, and the same alpha lipoprotein fractions as percentages of the total and so on, before coming to grips with the main issue. The final assessments are not startling, or clearly conclusive, but they are interesting and provocative. In brief, the total serum cholesterol level of Finns is high and climbs with age (to 280 mg. per 100 ml. or so), but is the same in hypertensives and controls. Hypertensives tend to show age changes earlier than controls and to carry more of their lipoproteins in the beta form, especially in malignant hypertension. Severe changes in retinal vessels are associated with raised cholesterol levels and increased beta lipoproteins in women but not in men. It would still appear that, whatever the truth of the lipid theory of atherogenesis may be, hypertension damages arteries mainly by brute force.

[1] "Studies on Serum Lipids and Lipoproteins in Hypertension", by Eliel Waris; *Acta Medica Scandinavica*, Supplement 337; accompanies Vol. 161; 1958. 9¼" × 6⅛", pp. 80, with illustrations.

Abstracts from Medical Literature.

THERAPEUTICS.

Thrombo-embolism.

J. M. MOSER (*J. Amer. med. Ass.*, August 2, 1958) describes a new therapeutic approach to thrombo-embolism by thrombolysis with fibrinolysin ("Plasmin"). The author states that the anticoagulant drugs do not provide a full answer to thrombo-embolism. They may prevent the extension or recurrence of the thrombus, but they do not remove it, the thrombus remains. In recent years fibrinolytic agents have been found to promote the dissolution of the fibrin framework on which a thrombus is supported, and should be capable of dissolving thrombotic material. Streptokinase was the first fibrinolytic agent, but it is not reliable; trypsin was similarly ineffective in dissolving thrombi. Fibrinolysin was next investigated; this substance can be obtained by activation of profibrinolysin obtained from the globulin fraction of the plasma proteins. Streptokinase added to profibrinolysin produces fibrolysin, and the streptokinase can then be removed. Fibrinolysin has been shown to dissolve arterial and venous thrombi in dogs, rabbits and humans. Fifty-two patients with various forms of thrombo-embolic disease were treated by intravenous infusions of a preparation of fibrolysin in doses up to 90,000 fibrinolytic units. An increase in the patients' fibrinolytic activity was shown by determinations of the rate of dissolution of a standard fibrinogen-thrombin clot. The author presents detailed reports on 10 patients who obtained symptomatic relief. Hæmorrhages did not occur, and disturbance of blood coagulating factors was minimal. Fever followed the infusion in 25 patients. It is suggested that anticoagulant drugs should be used to prevent recurrence of the thrombosis.

Reactions to Poliomyelitis Vaccine.

M. C. TIMMERMAN (*J. Amer. med. Ass.*, August 9, 1958) reports reactions, usually urticarial, in patients given injections of poliomyelitis vaccine. These were thought to be due to traces of penicillin in the vaccine since each patient had had a similar reaction due to penicillin allergy. Each patient recovered quickly after a penicillinase injection, and no recurrence followed subsequent doses of a brand of vaccine which did not contain penicillin. The author recommends that patients with previous penicillin allergy should receive penicillin-free vaccines, or penicillinase should be given prophylactically preceding the vaccine injection. The vaccine contains the following substances which could cause reactions: monkey protein, horse serum, formaldehyde, preservatives and antibiotics.

Oxytetracycline for Leptospirosis.

R. W. R. RUSSELL (*Lancet*, November 29, 1958) describes the result of a controlled trial of oxytetracycline in the treatment of leptospirosis. The trial was conducted on 52 consecutive patients admitted to a military hospital in Malaya; the patients were servicemen who had contracted leptospirosis while on duty in the jungle. The diagnosis was confirmed in all cases by blood culture or serological tests. Treatment consisted of an initial dose of 1·5 grammes, followed by 0·5 gramme every six hours. If persistent vomiting prevented oral administration, the drug was given intravenously. The treatment group contained 27 patients, and the control group 25, who were given ascorbic acid tablets as a placebo. It was found that treatment with oxytetracycline shortened the average duration of pyrexia from 6·4 to 2·5 days, and the duration of symptoms from 6·9 to 4·0 days after treatment had been begun. There was no significant difference between the two groups in the incidence of jaundice or of renal complications. There were no significant toxic effects attributable to oxytetracycline. There was an average delay of 3·9 days between the onset of symptoms and the beginning of treatment, and the authors consider that this interval is not likely to be reduced in practice elsewhere. They conclude that, for the present, oxytetracycline or penicillin in high dosage remains the treatment of choice in this condition.

Sulphamethoxypyridazine.

A. RAVINA (*Presse méd.*, October 15, 1958) presents a statement, based on many available reports, on the use of sulphamethoxypyridazine, a slowly excreted sulphonamide. He states that, in spite of the introduction of many new antibiotics, those who favour the use of the sulphonamides consider that they continue to provide treatment low in cost, easy to administer, and of low toxicity. After the administration of sulphamethoxypyridazine, the blood level rapidly reaches a high figure, and an effective therapeutic level is maintained for prolonged periods, sometimes as long as 96 hours. Thus doses of this agent may be given at long intervals, generally only once in 24 hours. The chief therapeutic indications are urinary infections, acute infections of the respiratory tract, naso-pharyngeal infections, otitis media and furuncles. It is in general well tolerated, though the usual safeguards must be observed in the treatment of allergic patients, as well as those with renal insufficiency, and the blood picture must be watched if treatment is prolonged.

"Preludin" for the Obese Diabetic.

W. LEITH AND J. C. BECK (*Canad. med. Ass. J.*, December 1, 1958) report on the use of phenmetrazine hydrochloride ("Preludin") for the obese diabetic patient. They state that the value of this drug in weight reduction is well attested; it has sympathomimetic properties closely allied to those of ephedrine and amphetamine, and acts as an anorexic agent, with minimal side effects on the central nervous and cardiovascular systems. Thirty obese patients with proved diabetes mellitus were selected for trial. Their ages ranged from 41 to 81 years. Fifteen of the group required daily insulin injections, varying from 16 to 60 units of protamine zinc insulin; in the remainder the diabetes was controlled by diet alone. All were overweight, and in all of them their weight had been either stationary or slowly increasing before the trial began. It was a double-blind trial, using phenmetrazine or a placebo in alternate months; the dosage of phenmetrazine was 25 mg. three times a day, 15 minutes before meals. Ten of the patients failed to cooperate, but 15 of the remaining 20 showed a substantial weight loss while taking phenmetrazine; no weight was lost during the periods when the placebo was being taken. Blood sugar levels and insulin requirements were not significantly affected by the treatment, though one patient showed a definitely hyperglycæmic effect which might have been attributed to the phenmetrazine. In only five patients was a fall in blood sugar levels demonstrated in association with weight loss. The authors conclude that phenmetrazine hydrochloride has little or no effect on blood sugar levels when taken in this dosage, and that it is a potentially useful tool in the long-term management of the obese diabetic patient.

Antibiotics and Bacterial Hydrolysate.

A. RAVINA (*Presse méd.*, November 29, 1958) states that several Italian workers have, during the past two years, recommended the combination of antibiotics with a bacterial hydrolysate in the treatment of certain acute infections. He has made a trial of the method, and reports his results. Neither in human infections nor in experimental infections were results comparable with those recorded by the Italian workers obtained. He does not consider that the addition of a bacterial hydrolysate to the classical penicillin-streptomycin combination reinforced the action of the latter. He believes that, under present conditions of therapy, it is useless to try to add to the antibiotics an agent designed to stimulate the natural defence mechanisms.

Antibiotics in the Treatment of Constipation.

A. RAVINA (*Presse méd.*, October 25, 1958) has found that a number of antibiotics, particularly tetracycline and neomycin, given by mouth in moderate or small dosage, relieve constipation for long periods, or even effect a permanent cure of the condition. In some cases the treatment must be accompanied by the exhibition of bismuth subnitrate and small doses of antispasmodics. It is in general very well tolerated. The author states that investigation of the mode of action of this treatment is desirable.

Stokes-Adams Syndrome.

R. T. JONES (*J. Amer. med. Ass.*, August 9, 1958) describes medical control in a case of Stokes-Adams syndrome. Before the diagnosis was established, the patient, a man aged 40 years, had been treated with anti-convulsant drugs. The condition was a sequel of rheumatic fever, and syncopal attacks were occurring at frequent intervals. When the diagnosis was established ephedrine was given in doses of 30 mg. every three hours, isoproterenol 20 mg. every two hours sublingually, and hydroxyamphetamine hydrobromide ("Paredrine") 40 mg. every four hours. As this failed to give complete control of the attacks, isoproterenol was

then given intravenously by continuous drip transfusion, at a strength of 0·5 mg. per 100 ml.; at the same time the administration of prednisone was commenced at a dosage of 40 mg. daily. This controlled the attacks as long as the transfusion was maintained at a rate of 20 drops per minute (5 µg. per minute). After one week of this therapy it was possible to reduce the dosage and change to 15 mg. of proterenol given sublingually every three hours. The dosage of prednisone was gradually reduced over a period of six weeks, but attacks recurred three weeks after its complete withdrawal. For a time the attacks were controlled by the administration of 15 mg. of prednisone per day, but eventually it was decided to stabilize the rhythm in a continuous atrio-ventricular block. To this end prednisone and isoproterenol were withdrawn, and neostigmine was instituted in doses of 15 mg. every three hours. This fixed the block, which thereafter remained stable with a ventricular rate of 36 to 40 systoles per minute.

PATHOLOGY.

Diagnosis of the Cause of Death.

E. Waaler and M. Grimstvedt (*Acta path. microbiol. scand.*, fascicle 4, volume 43, 1958) have evaluated the reliability of clinical diagnoses of the cause of death by comparing the clinicians' diagnoses with the post-mortem findings in 783 cases in which malignant disease was revealed at autopsy. A correct clinical diagnosis had been made in 62% of cases, in 10% the diagnosis was doubtful, and in 18% the diagnosis was wrong. Malignant tumours were incidental findings and not related to the cause of death in 6% of these autopsies, and in 1·6% the site of the primary growth was uncertain. In general, carcinomata situated in the breast, uterus and œsophagus, as well as the leukæmias, were correctly diagnosed when they were the cause of death, whereas tumours of internal organs were correctly recorded in only 50% to 60% of cases. Diagnostic errors were common in patients dead from carcinoma of the liver, gall-bladder, bile ducts, duodenum or pancreas.

The Kidney in Treated Malignant Hypertension.

L. J. McCormack *et alii* (*Amer. J. Path.*, November-December, 1958) have compared the renal vascular lesions in patients with malignant hypertension treated by hypotensive drugs with those in the untreated. The material for the study was obtained from the kidneys of 100 subjects seen at necropsy, of whom 19 had been treated by antipressor drugs. Treated patients, especially those who had been under therapy for long periods of time, almost always exhibited healing of the acute lesions. Although thrombosis and thrombonecrosis of arterioles and glomerular necrosis were no longer seen, there were changes in large and medium sized vessels which presumably led to the more slowly progressive renal failure which caused death in most of the treated patients. These changes consisted of subintimal fibrosis which produced narrowing, and in some cases occlusion, of the arterial lumen. These lesions are thought by the authors to reflect damage done to the vessel prior to treatment and are paralleled by similar lesions in hypertensive rats treated by powerful antipressor agents.

Bronchiolitis Obliterans.

T. J. Moran and H. R. Hellstrom (*A.M.A. Arch. Path.*, December, 1958) have produced bronchiolitis obliterans in rabbits by injecting dilute nitric acid into the trachea. Both the acute disease and the chronic form corresponded closely to that found in humans after exposure to certain war gases, and fumes of nitric and sulphuric acids, and in silo-filler's disease. The first demonstrable change is hæmorrhage from the capillaries of the respiratory bronchioles. This is followed by necrosis and desquamation of the bronchiolar epithelium, with formation of coagulum-filled epithelium-covered papillary processes in about 12 hours, fibroblastic activity in about three days, and definite scar tissue in two weeks. Regeneration of morphologically differentiated bronchiolar epithelium is present in some animals in 24 to 36 hours. The use of combinations of penicillin and streptomycin, or of cortisone, penicillin and streptomycin, did not affect the survival rate of the animals, approximately two-thirds of which died from acute pulmonary œdema or chemical pneumonia. A combination of penicillin and streptomycin did not influence the development of bronchiolitis obliterans in surviving animals, but a combination of cortisone, penicillin and streptomycin prevented bronchiolitis obliterans in all but one of 12 surviving rabbits to which it was administered. The administration of cortisone was begun the day prior to the injury. The effect of cortisone in preventing bronchiolitis obliterans and the demonstration of the progression of the lesions at various time intervals support the concept that bronchiolitis obliterans develops from repair by fibrosis of the initial damage to the bronchiolar epithelium rather than from long-continued inflammation of the bronchiolar wall. Therapeutic implications of the use of cortisone, especially its immediate employment, in human beings exposed to chemical irritants known to produce bronchiolitis obliterans are discussed.

Cytological Considerations in Some Highly Malignant Cancers.

G. Castelain and C. Castelain (*Presse méd.*, October 1, 1958) present the results of a study carried out at the Curie Foundation, Paris, on the cytology of highly malignant and rapidly growing cancers. They state that they have been struck, in the course of interpreting a great number of cancer cytograms, by the different appearance of the nuclei of malignant cells according to the type of tumour, and also by the predominance of a specific nuclear type in a given cancer. As a result of their observations they put forward a cytological classification of nuclei of cell tumours in four grades—A, B, C and D. They have also attempted to establish a relationship between the type of nucleus and the outcome of the illness in each case studied. The tumours in the cases presented comprised atypical epitheliomata, melanomata and a sarcoma, all progressed rapidly, and all fell indisputably in grade D of the nuclear classification. The authors state that this grade D is characterized by considerable enlargement of the nucleus with exaggerated staining of the nucleoli. This type of nucleus does not belong to any particular anatomical type of tumour. It is found in epitheliomata of different organs (skin, mucous membrane, breast, uterus), as well as in tumours of the conjunctiva. It is not found in the œdema and vacuolation produced by X rays. It is found in patients of all ages, but more frequently in young subjects, in whom the progress of cancers is generally more rapid; however, it is found in aged patients, and then has the same significance. The nuclear type of a tumour appears to be fixed, and does not seem to alter during the progress of the disease. However, the authors state that this point requires repeated control studies. They recommend prolonged and systematic study of these nuclear types, since they believe that cytological investigation of tumours according to the classification they have evolved is of value in establishing the remote prognosis, and emphasizes the importance of alterations outside the chromosomes of cancer cells.

Cholagogues and Liver Necrosis.

G. R. Cameron and S. M. Hasan (*J. Path. Bact.*, October, 1958) have found that increasing the flow of bile while liver-cell necrosis is developing is likely to accentuate that necrosis. The authors could not say whether this conclusion applied to human conditions, but they suggest that rest from secretory activity during hepatitis may be beneficial to the liver.

Osgood-Schlatter's Disease.

G. D. La Zerte and I. H. Rapp (*Amer. J. Path.*, July-August, 1958) have examined nine specimens from patients with Osgood-Schlatter's disease, and their conclusion is that aseptic necrosis is not the original lesion. There is avulsion of part of the tibial tuberosity, as described originally by both Osgood and Schlatter, and the avulsed fragment may then undergo necrosis or be remodelled and enlarged. The lesion seems to be due to trauma caused by pull of the quadriceps tendon on the apex of the tibial tuberosity.

Pneumotoxic Pneumonia.

J. Read (*J. Path. Bact.*, October, 1958) prepared an anti-rat-lung serum which he found would cause characteristic lesions in the lungs when administered by the intratracheal route. There was early hæmorrhage and exudation of neutrophils and eosinophils followed by active mononuclear-cell proliferation. This led to thickening of alveolar septa with granulomatous buds protruding from the alveolar walls. Tissue necrosis was rare and arteritis was not a feature. The lesions either resolved completely or proceeded to fibrosis with occasional focal collapse and intra-alveolar organization. The lesions in general were reminiscent of those seen in conditions such as polyarteritis nodosa, Wegener's granulomatosis and other conditions causing fibrosing pneumonitis with granulomata.

Brush Up Your Medicine.

STEROID HORMONES IN CLINICAL MEDICINE: I. CORTICOSTEROIDS.

A STEROID may be defined as a substance which contains the ring structure shown in Figure I. The most important steroids of the body include the sex hormones (androgens, œstrogens and progesterone) and the corticosteroids. Corticosteroids are those steroids secreted by the adrenal cortex which exert their principal actions upon carbohydrate metabolism or upon the metabolism of minerals and water.

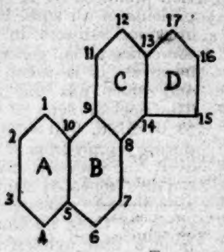

FIGURE I.

According to the relative importance of these two actions, corticosteroids are divided respectively into glucocorticoids and mineralocorticoids. The most important glucocorticoid of the body is hydrocortisone (cortisol); the important mineralocorticoid is aldosterone, although deoxycorticosterone is more widely used because it can be prepared much more readily. This paper is confined to the clinical use of corticosteroids and their derivatives.

It should be realized that the carbon atoms, which are indicated by number in the formula above, are joined by single bonds, and that their remaining valencies are occupied by hydrogen atoms as shown in Figure II.

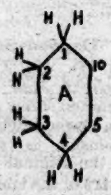

FIGURE II.

Of these two hydrogen atoms, one is called α and the other β. Some of the hydrogens can be replaced by other groups or atoms, and it is the number, nature and position of these "foreign" substituents which give to each steroid its chemical and physiological individuality. Certain substituents are present in all corticosteroids, and without the changes in the original steroid nucleus shown in Figure III, corticosteroid activity is not possible. In this formula:

| means CH_3

The CH_3 is understood in order that the formula will not appear unnecessarily complex; hydrogen atoms are omitted for the same reason.

The Use of Steroid Hormones in Clinical Medicine.

In clinical medicine, corticosteroids (hereafter referred to as steroids) have two principal uses—namely, (i) as replacement therapy in endocrine diseases (e.g., Addison's disease) and (ii) as a means of influencing the natural history of certain diseases, the ætiology of which is not directly attributable to abnormal adrenocortical function. The use of steroids in the treatment of female pseudohermaphroditism requires special mention since it belongs to neither group. In this case one property of the steroids—namely, their capacity to suppress the secretion of ACTH by the pituitary—is used in order to control the excessive production of this hormone. An enzyme defect interferes with the capacity of the adrenal cortex to secrete glucocorticoids; this in turn leads to an increase in the release of ACTH from the pituitary, and the stimulating effect of this ACTH promotes the secretion of excessive quantities of adrenal androgens (there being no impediment to the production of androgens). The administration of cortisone not only replaces the missing glucocorticoid, but controls the production of ACTH and hence of adrenal androgens. The dosage of cortisone required is large but variable, and the maintenance dose is regulated according to the level of urinary 17-ketosteroid output.

In other endocrine diseases the use of steroids is aimed at replacing the normal production of corticosteroids by the

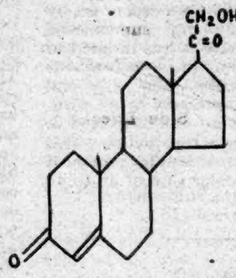

FIGURE III.

adrenal glands. The mineralocorticoid activity of glucocorticoids is such that it is not usually necessary to administer deoxycorticosterone. The commonest indications for steroid replacement therapy are: (i) hypopituitarism, (ii) Addison's disease, (iii) after hypophysectomy or bilateral adrenalectomy. Here the value of steroid therapy is beyond dispute, and dosage is low (e.g., 25 mg. of cortisone given daily by mouth may suffice). Undesirable side effects of steroid therapy are not usually encountered in this context because the doses used are small and merely serve to replace the glucocorticoids normally secreted by the adrenal cortex. For the same reason, the particular steroid used is of no great importance. Any glucocorticoid, or any modification of the natural glucocorticoids which possesses sufficient glucocorticoid and mineralocorticoid activity, will serve the purpose. Cortisone itself is perfectly satisfactory and can be taken by mouth; prednisone and other derivatives of cortisone have no special virtues for replacement therapy. It is not usually necessary to prescribe deoxycorticosterone in cases of Addison's disease; but in cases of hypopituitarism, thyroid extract and sex hormones are indicated. It must always be kept in mind that replacement therapy may require an abrupt increase in dosage during or after exposure to stressor stimuli (fever, anæsthetics, vomiting, diarrhœa, infection, etc.).

In the second use of steroid therapy, clarity gives way to confusion. Not only are the exact indications for steroid therapy a matter of dispute, but the dosage, duration of treatment, type of steroid and particular form of a given disease most likely to respond to steroids are all matters upon which opinions differ. Moreover, under these conditions much larger doses of steroids are required, and hence toxic manifestations are more frequently encountered. Since these toxic signs form one of the most important limiting features of steroid therapy, chemists have exercised their ingenuity in the hope of improving the hormones available for clinical use. Such improvements are directed at enhancing the suppressive action of steroids upon the inflammatory and allergic reactions of the body at the expense of such undesirable effects as salt retention, œdema, obesity of the type seen in Cushing's syndrome, hyperglycæmia, osteoporosis and androgenic manifestations.

In general, the use of steroids in such diseases is empirical, but it is believed that the value of these hormones lies in their capacity to suppress those responses to disease which are likely to lead to permanent damage or to acute distress; so that, when the causative factors have burnt themselves out and steroid therapy is withdrawn, the permanent scars of the disease will have been avoided, and acute distress will not return. This at least is the working hypothesis upon which steroid therapy in collagen diseases and asthma is based. In diseases such as hæmolytic anæmia, thrombo-

cytopenia and nephritis type II, the rationale of steroid therapy is even more obscure.

No doubt it will turn out that the many actions of cortisone can be reduced to a few fundamental effects; but until these effects have been carefully defined, it will not be possible to say how far it is theoretically possible to reduce the undesirable side effects of such a steroid without destroying its therapeutic properties. Thus the thin skin, red face, fragile capillaries and osteoporosis seen during cortisone therapy are due to the action of the hormone upon protein metabolism. How far are the desirable actions (e.g., suppression of inflammatory reaction and of scar tissue) directly or indirectly attributable to this effect upon protein metabolism? With cortisone itself it was soon realized that large doses inevitably produced side effects, but small doses could be used indefinitely without their appearance. This encouraged a search for steroids which were more powerful (weight for weight) in suppressing inflammation than cortisone, in the hope that, if used in smaller doses, they would prove effective but less toxic. In some measure this hope has been justified.

Side Effects.

The following changes are some of the most frequently encountered and serious side effects of steroid therapy:

1. Adiposity with a distribution like that seen in Cushing's syndrome.
2. Electrolyte disturbances involving retention of sodium and loss of potassium.
3. Diabetes.
4. Androgenic manifestations, including acne, hirsutism, keratosis pilaris and menstrual irregularities.
5. Protein catabolic effects, including purple striæ, bruising, osteoporosis and fractures.
6. Thrombosis.
7. Mental changes, including depression and paranoia.
8. Peptic ulcer.
9. Masking of the signs and symptoms of some underlying disease, e.g., appendicitis or tuberculosis.

Synthetic Steroids.

Among the changes which chemists have produced in the structure of steroid hormones, the following have shown themselves worthy of clinical trial: (i) halogenated compounds, (ii) Δ^1 derivatives, (iii) methylated derivatives, (iv) hydroxy derivatives.

Halogenated Derivatives.—When a halogen atom is introduced at the 9 α position, the resulting corticosteroid shows enhanced glucocorticoid and mineralocorticoid activity. The most useful of these halogenated compounds is 9 α-fluorohydrocortisone, which shows five times the mineralocorticoid activity of deoxycorticosterone and ten times the potency of hydrocortisone in regulating carbohydrate metabolism. Even greater increase in anti-inflammatory properties is seen. The intense salt-retaining properties of these compounds have prevented their use in the treatment of the second group of diseases mentioned above, and 9 α-fluorohydrocortisone is reserved for two purposes—the treatment of female pseudohermaphroditism and the performance of tests of corticosteroid suppression. In the second case, the urinary 17-ketosteroid output is measured before and after administration of the hormone; the 9 α-fluoro derivative is given in such small doses (10 mg.) as to cause minimal addition to the urinary 17-ketosteroids, and thus any significant alteration in endogenous 17-ketosteroid production is revealed.

Δ^1 *Derivatives.*—When a double band is inserted between C_1 and C_2 by removal of two hydrogen atoms, the cortisone or hydrocortisone molecule becomes considerably more potent in its anti-inflammatory and carbohydrate-regulating properties, while salt retention becomes negligible with therapeutic doses. Prednisone is the name given to the Δ^1 derivative of cortisone, and prednisolone is the analogous derivative of hydrocortisone. These two steroids are almost identical in their physiological properties and represent one of the most successful modifications of natural steroids. In addition, they exert a more prolonged action than cortisone, and in comparable doses they are less likely to cause salt retention, diabetes and moon-face. The most undesirable side effect encountered with these two steroids is dyspepsia. Even in small doses prednisone stimulates the secretion of hydrochloric acid in the stomach, so that indigestion in one form or another is an almost universal complaint. If these steroids are to be prescribed for longer than a few days, the concomitant administration of antacids is advisable. Manufacturers have met this problem by combining prednisone with an alkaline powder in one and the same tablet.

Methylated Derivatives.—A number of new steroids have been prepared by replacing a hydrogen atom with a methyl group at various positions of the nucleus. The compound 16 α-methyl, 9 α-fluoroprednisolone is one of the most promising methylated steroids. This substance is more potent in its anti-inflammatory properties and is less likely to produce side effects than prednisolone. The claim that 16 α-methyl, 9 α-fluoroprednisolone is less likely than other steroids to cause dyspepsia, if verified, will be of great value. Similar changes in the action of prednisolone are produced by 6-methylation.

Hydroxy Derivatives.—The most versatile and promising steroid yet to be synthesized is 9 α-fluoro, 16 α-hydroxyprednisolone. In this steroid, hydroxylation mitigates the salt-retaining effect of 9-halogenation, and in therapeutic doses electrolyte disturbances are not encountered. It is also claimed that this preparation causes no disturbance of psychic equilibrium, and that its use is rarely complicated by peptic ulcer or osteoporosis.

Indications for Steroid Therapy.

Collagen Diseases.—Rheumatic fever and rheumatoid arthritis are among the diseases in which steroid therapy has been particularly successful. The hormones protect the body from the ravages which usually follow these diseases. Lupus erythematosus, scleroderma, dermatomyositis and periarteritis nodosa are examples of collagen diseases which may respond to steroid therapy. Here the plan of treatment is to use large doses of the hormone early in the diseases and to await a natural remission, in this way protecting vital organs from permanent damage. In scleroderma and dermatomyositis the results of such treatment have been disappointing. The acute stages of gout can be cut short by means of cortisone therapy, but the drug is usually reserved for severe cases.

Skin Diseases.—In those skin diseases in which allergic factors are believed to play an important ætiological role (infantile eczema, atopic dermatitis and neurodermatitis), steroid therapy has shown excellent results. Again the course of the disease is altered by suppression of the allergic phenomena until such time as spontaneous remission occurs. In milder cases local application of steroids is sufficient. Pemphigus, formerly resistant to all forms of treatment, is often held in abeyance by steroid therapy, although large doses are required for long periods if relapse is to be avoided. This is the disease in which side effects are especially troublesome, but such is the nature of pemphigus that the price is not too high to pay for a remission.

Diseases of the Eye.—Steroid therapy has revolutionized the management of iritis, iridocyclitis and choroiditis. By reducing cellular exudates, inhibiting the formation of granulation tissue and suppressing fibroblastic repair, steroids protect the eye from the permanent scars of these diseases. Moreover, local application is ideal for superficial lesions, although systemic administration is required for such conditions as choroiditis. It is most important to keep in mind the need for concomitant administration of an antibiotic if the presence of infection is suspected.

Status Asthmaticus.—When status asthmaticus fails to respond to the usual measures, intramuscular administration of cortisone will usually cut short even the most severe attack. The place of oral steroid therapy in the long-term management of asthma is disputed.

Blood Diseases.—Acquired hæmolytic anæmia and thrombocytopenic purpura sometimes respond to steroid therapy, but the results are variable.

Diseases of the Alimentary Canal.—Improvement has been reported following local and systemic administration of steroids in ulcerative colitis, but again the response is by no means invariable. In hepatitis it is hoped that steroids may mitigate the development of scar tissue and so reduce the tendency to produce hepatic fibrosis. That it does so remains to be proven.

Burns.—Steroid therapy has found a limited place in the emergency treatment of extensive burns. The hormones are helpful in combating shock and may reduce scarring.

Contraindications.

The systemic administration of cortisone should be avoided in cases of tuberculosis and other infections unless these are controlled by antibiotics during steroid therapy. Hyper-

tension, cardiac failure, psychoses or a history of severe nervous breakdowns should be regarded as relative contra-indications, and steroid therapy must be used with caution in the presence of peptic ulcers, osteoporosis and diabetes mellitus. The chief contraindication to local therapy is infection in the lesion to be treated.

Administration and Dosage.

Oral.—For most purposes oral administration is the method of choice when steroids are to be used systemically. As substitution therapy there is little to choose between the various preparations; but when large doses are to be used, prednisone or 16 α-methyl, 9 α-fluorohydrocortisone is to be preferred. Prednisolone and prednisone are interchangeable. In collagen diseases, blood diseases and hepatitis, prednisone is given in doses of 40 to 80 mg. for the first few days until evidence of remission is seen; thereafter the dose is gradually reduced until, at the end of two weeks, a suitable maintenance dose is found such as to control symptoms and avoid side effects (usually 10 to 20 mg. daily). In pemphigus, lupus erythematosus, rheumatic fever and blood diseases this programme may not be possible, in which case large doses (80 to 120 mg.) are necessary for long periods, and side effects are inevitable. In these circumstances each patient presents a different problem, and the physician must ask himself if the price of side effects is worth the remission produced. These preparations of steroids for oral use act in about four hours, and their effects last from six to nine hours; division of the daily dose is therefore essential.

TABLE I.

Trade Name.	Chemical Name.	Preparations.	Dosage.[1]
"Cortisyl." "Sheroson."	Cortisone acetate.	Tablets. Aqueous suspension (25 mg. per ml.).	25 mg.
"Hydrocortisyl." "Sheroson F."	Hydrocortisone.	Tablets. Aqueous suspension (25 mg. per ml.). Lotion. Ointment. Eye drops 1%. Eye ointment 0·5%, 1%, 2%.	25 mg.
"Decortisyl." "Delta-Scheroson." "Metacorten."	Prednisone.	Tablets. Aqueous suspension (5 mg. per ml.). Lotion. Ointment. Eye drops 1%. Eye ointment 0·5%, 1%, 2%.	5 mg.
"Metacortelone." "Paracortol." "Precortisyl." "Scherisolon."	Prednisolone.	Tablets. Aqueous suspension (5 mg. per ml.). Lotion. Ointment. Eye drops 1%. Eye ointment 0·5%, 1%, 2%.	5 mg.
"Pregnenolone."	—	—	—
"Percorten." "Primocort."	Deoxycorticosterone.	Solution for intramuscular injection.	—
"Decadrol." "Deranil."	9α-fluoro, 16α-methylprednisolone.	Tablets.	0·8 mg.
"Ledercort" (Triamcinolone).	9α-fluoro, 16α-hydroxyprednisolone.	Tablets.	2 mg.
"Medrol."	6-methyl prednisolone.	—	4 mg.

[1] The relative doses of the steroid tablets listed are calculated on the basis of the anti-inflammatory properties of the hormones when compared with cortisone.

Intramuscular.—The same steroids are administered intramuscularly when vomiting or diarrhœa is troublesome, in the treatment of status asthmaticus and sometimes of acute gout, and when steroids are used before or after operation. Dosage is the same as for oral use.

Intravenous.—For emergency treatment (e.g., Addisonian crisis) hydrocortisone can be given intravenously in doses of 50 to 100 mg.

Local.—Local administration of steroids is useful in diseases of the eye, when drops containing 10 to 25 mg. of hydrocortisone per ml. are instilled every second hour. For application to skin lesions a preparation containing 10 mg. of hydrocortisone in one gramme of lotion or ointment is used, and in diseases both of the eye and of the skin an antibiotic can be combined with the steroid if the presence of infection is suspected. For intraarticular administration hydrocortisone (25 to 100 mg.) is used.

Table I indicates the steroids in common use in this country and gives the relative dosage.

Conclusion.

In conclusion, it should be emphasized that the decision to prescribe steroid hormones systemically or locally should be deliberate and, where possible, based upon accurate diagnosis. The casual prescription of steroids as a therapeutic trial is to be condemned, and half-hearted doses diluted by analgesics, in the form of combined tablets of aspirin and predisone, etc., have no place in steroid therapy.

PETER HALL.
Sydney.

British Medical Association.

VICTORIAN BRANCH: SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on May 7, 1958, at the Alfred Hospital. The meeting took the form of a series of clinical demonstrations arranged by the Alfred Hospital Clinical Society.

Symptomless Extreme Renal Failure.

DR. MORRIS C. DAVIS showed patients to illustrate the syndrome of "silent" advanced renal failure. In his presentation he pointed to a need for reorientation of the present knowledge of renal disease. He said that the observation that advanced morbid pathological changes might be present when there were few or no symptoms was no better illustrated than in those conditions associated with gradual insidious renal destruction.

The first patient was a man, aged 37 years, who had been apparently well even at the time of his admission to hospital, some nine weeks previously having noticed some breathlessness at night; with it he noticed palpitation and "bubbling" in the chest, for which he sought medical advice. The condition was ascribed to bronchial asthma and he was given some "Ephedrobarbital" without relief. He remained confined to bed for four weeks, by which time he was well, but a little apprehensive. His blood pressure fluctuated, and at one time was observed to be 270/124 millimetres of mercury. It was because of that finding that the patient was referred to hospital for observation. He was otherwise symptomatically well. Inquiry into his past history revealed that about six years earlier he had suffered an attack of left loin pain associated with frequency of micturition and some scalding; the attack had lasted for six days. A vague "out of sorts" feeling 18 months prior to his admission to hospital had resulted in a check-up for pulmonary tuberculosis, which gave negative findings. Apart from that and the recent episode he had been completely well, carrying out his work as a steeple-jack without any difficulty. On the day of his admission to hospital he stated that he was entirely free of symptoms and he was not able fully to understand the reason for hospitalization.

On examination he presented as a healthy-looking young man. There was a soft grade 1 to 2 mitral systolic bruit, his blood pressure was 230/120 millimetres of mercury, and variable slight to moderate albuminuria was present. The specific gravity of the urine was 1008, and microscopic examination revealed six to eight red blood corpuscles per high-power field and an occasional polymorph. Examination of the ocular fundi revealed just perceptible hypertensive changes. It was considered that albuminuria, hypertension and left ventricular disturbance could appear together only in a condition of long standing, and a diagnosis of advanced renal failure was made. Indeed, before biochemical tests were performed a clinical assessment of 25% clearance was suggested. The urea clearance test in fact carried out next day revealed 26% renal function, with urea concentrations of 1·7 grammes per 100 cubic centimetres. A second test

three weeks later likewise gave a clearance value of 23%. That the clearance was a reasonable indication of renal function was shown by subsequent intravenous pyelography which revealed marked impairment of left renal function, the left pelvi-calycine system being sketchily seen. No ureteric obstruction was present, and the bladder was normal. Retrograde pyelography revealed a non-functioning left kidney. Investigation of the functioning right kidney revealed a urea clearance of 23%.

During the period of hospital observation the patient suffered frequent temperature rises to 101° F. which, when apparent, were associated with dysuria. He was otherwise free of symptoms, and left hospital ambulant and well six weeks after his admission.

Blood pressure readings taken from that time revealed figures of 270/180 millimetres of mercury on three occasions and 248/136 millimetres of mercury. Each time he presented at the hospital for review, careful questioning always met the same response—he was apparently healthy and symptom-free. Always the blood pressure finding would come as a sharp surprise, the renal function test results even more so.

Some two weeks prior to the meeting he developed a sudden pain in the right loin, for which he was again admitted to hospital. He was otherwise again free of any of the usual symptoms of renal failure—no dysuria and no headache, until after the attack of pain. With the onset of pain vomiting had occurred, and on his admission to hospital his blood urea level had risen to 125 milligrammes per 100 millilitres. With abatement of pain and vomiting, the blood urea level rapidly returned to normal.

Dr. Davis said that the characteristic rapid rise of blood urea level with a minor fluid balance disturbance—transient vomiting—was a feature of reduced renal reserve, and commonly found in that disease. As observed at the meeting, the patient appeared to be a healthy male—robustly healthy—with a blood pressure of 270/166 millimetres of mercury and mild albuminuria and pyuria.

The second patient, a man, aged 53 years, had played 36 holes of golf on the day prior to his admission to hospital. Before that date he had felt mildly out of sorts for a few months, but had carried on his work as a traveller, which necessitated his covering long distances by motor-car. Recently he had noticed a mild occasional headache and inability to keep his food down occasionally in the mornings. There had been some cramp—he noticed that his hand tightened up—and lately he had suffered violent cramps of the legs while in bed. There had been no dysuria, but albuminuria was present and was said to have been discovered some years earlier. The clue to his lesion was found in a history of hæmaturia at the age of 10 years, which had been accompanied by renal pain; but after the age of 12 years he had not suffered any such attack.

On examination of the patient, his blood pressure was 178/120 millimetres of mercury, moderate albuminuria was present and there were some pus cells in the urine, but no casts. In view of his recent morning nausea, and despite his ability to play 36 holes of golf the day before, he was admitted to hospital with the diagnosis of urgent renal failure. Renal function tests revealed urea concentrations of 1·1, 1·1 and 1·0 grammes per 100 millilitres; the blood urea content was 210 milligrammes per 100 millilitres, and the clearance was under 10%. During the time of waiting for a bed the patient's vomiting was more marked, and within two days of that time he was semi-stuporose and in a state of advanced uræmia; the blood urea content was then 260 milligrammes per 100 millilitres. His deterioration was so rapid that from a virtually symptom-free, ambulant state, the onset of more severe vomiting resulted in the production of a terminal condition. Death occurred eight days after his admission to hospital. Dr. Davis showed specimens illustrating long-standing pyelonephritis with massive renal destruction.

Dr. Davis then presented synopses of four other illustrative cases. (i) A patient, aged 57 years, had recurrent pyelitis, then a recent history only of cramps; the blood urea content was 315 milligrammes per 100 millilitres. (ii) A patient, aged 37 years, had severe anæmia, but was ambulant; death occurred within 14 days of admission to hospital. A polycystic kidney was found at autopsy. (iii) A patient, aged 21 years, had suffered from Ludwig's angina at two years of age; advanced renal failure was present, but there were no symptoms. (iv) Twin sisters, aged 54 years, each with polycystic kidneys, were ambulant and well with blood urea contents of 280 milligrammes per 100 millilitres.

Dr. Davis said that the cases presented illustrated the picture of chronic renal destruction. The essential features were (*a*) relative absence of symptoms, (*b*) tell-tale albuminuria variable, (*c*) moderate rise of blood pressure, (*d*) occasional pus cell in the urine, (*e*) cramps as an indication of electrolyte imbalance, (*f*) surprising quiescent cardiac enlargement, (*g*) surprisingly poor renal function and urea clearance, (*h*) rapid exacerbation with minor disturbances of fluid balance. The characteristic feature of all those cases was the slow, insidious destruction of renal tissue, and Dr. Davis considered that a new term "nephro-phthisis" or chronic renal destruction might well be worthy of introduction into the classification of the nephritides.

Dr. Davis suggested that the following classification would fulfil the requirements: (i) acute renal disease; (ii) subacute renal disease; (iii) chronic renal destruction—"nephro-phthisis": (*a*) destruction with fibrosis of parenchyma, (*b*) destruction by pus (might lead to fibrosis)—pyelonephritis, (*c*) destruction by cyst—polycystic kidney, (*d*) destruction by any morbid change (neoplasm or arterial disease), senility or arteriolitis (malignant). All, when slow and insidious, ultimately produced the same picture.

Phæochromocytoma.

Dr. Davis then showed a male patient, who had had a phæochromocytoma removed. He said that the case was presented because it revealed some of the difficulties of diagnosis of the true cause of hypertension. The patient, aged 15 years, had had constant headaches, worse with exercise, which occurred in attacks and were associated with photophobia. Earlier investigations revealed a blood pressure of 210/155 millimetres of mercury, cardiac enlargement, bilateral papillœdema and exudates, with features of severe arterial changes in the eye. Renal function tests showed good concentrating power, but a urea clearance of 50%. "Regitine" tests gave uninformative results.

Eighteen months later he presented with a blood pressure of 240/180 millimetres of mercury and severe headaches, with cardiac enlargement. The results of renal function tests were satisfactory and coarctation was excluded, so he was regarded as possibly suffering from phæochromocytoma and admitted to hospital for review. Special tests carried out by Dr. A. J. Barnett revealed that the "Regitine" test produced a classical drop in systolic and diastolic pressure. Intravenous pyelography showed deviation of the right ureter, and massage of the right loin produced a rise of blood pressure. Pressor amine excretion was greatly increased.

Operation was advised, and revealed a tumour in the right ureteric area about two inches in diameter. After its removal complete cure was achieved. At the time of the meeting the patient had a blood pressure of 118/80 millimetres of mercury and was completely well.

Charts of the course of the operation were presented to show the effect of handling the tumour and the operative and post-operative hazards.

Mitral Valve Disease.

DR. H. B. KAY showed three patients with mitral valve disease. The first illustrated the typical condition suitable for mitral valvulotomy; in contrast, a patient of similar age with mitral incompetence was regarded as suitable for plastic operation on the mitral valve. The third patient was a woman, aged 51 years, with mitral stenosis and aortic incompetence, who had had recurrent congestive cardiac failure for six years. At operation in July, 1957, satisfactory splitting of the mitral valve had been accomplished; she had had no recurrence of œdema since and needed minimal congestive cardiac failure measures.

Dr. Kay also discussed the records of a further five patients to illustrate difficulties encountered in assessment for operation.

Records of two patients with arrhythmias associated with acute myocardial infarction were demonstrated. The first, a man, aged 65 years, developed tachycardia on the fourth day and failed to respond to quinidine given by mouth and by intravenous administration; but sinus rhythm was established with the intravenous administration of 800 milligrammes of "Pronestyl". Two and a half years later he was well, and had no significant symptoms. The other patient, a man, aged fifty-nine years, developed ventricular tachycardia, which persisted for six weeks and then reverted to sinus rhythm, with reasonable recovery for three months; then sudden death occurred.

Finally Dr. Kay showed a woman, aged 66 years, with complete heart block and Stokes-Adams attacks in association with acute posterior infarct. The heart block was relieved with the use of aminophylline and adrenaline. Two years later she had had no recurrence of heart block, but was in persistent cardiac failure.

Nephrectomy in Renal Disease with Hypertension.

DR. DONALD G. DUFFY presented several cases illustrating the problems associated with the finding of unilateral renal

disease with hypertension and the possibility of treatment by nephrectomy.

The first case was that of a male, aged 38 years, who had suffered recurrent attacks of "urethritis" over a period of three years and later became hypertensive. Subsequent diagnoses over the years were recorded as "nephrosis", "nephritis" and "pyelonephritis". After 10 years, persistent azotæmia and unsatisfactory control of blood pressure levels with hexamethonium compounds characterized the course of his disease, while the suggested evidence of an atrophic right kidney at early intravenous pyelography was confused by a relatively normal retrograde pyelogram at subsequent examination, and nephrectomy was not considered necessary at that time. Death in cardio-renal failure occurred 12 years after the first urinary tract infection, and a kidney weighing half an ounce was found on the right side *post mortem*.

Dr. Duffy said that the case underlined the necessity for early and accurate diagnosis in the presence of recurrent urinary tract infection and the varying grades of albuminuria which occurred during the course of chronic pyelonephritis, as well as the fatal outcome of uncontrolled infection and hypertension.

Dr. Duffy's second case was that of a male, aged 45 years, who had suffered some 12 attacks of right-sided renal colic between the years 1942 and 1946. At operation in 1946, a hydronephrotic kidney was disclosed, for which an aberrant right renal vein was considered responsible, so that was ligated. His blood pressure was then 150/90 millimetres of mercury, and the urine was free of albumin and sterile. Subsequent pyelographic examination disclosed a persistent hydronephrosis on the right side, and in 1952 further right loin pain was experienced. His blood pressure was now 175/105 millimetres of mercury, the urine was free of albumin and sterile, and the results of renal function tests were normal. By 1955 the blood pressure had risen to 230/130 millimetres of mercury, higher diastolic pressures being recorded during that year. Right nephrectomy was performed in February, 1956, in the hope of arresting that progression. Subsequent to operation, his blood pressure fell to normal levels, only to climb over the next six months to the region of 170/110 millimetres of mercury, at which level it had since remained without the assistance of hypotensive therapy. Dr. Duffy said that the case illustrated the necessity for the removal of the diseased kidney as early as possible, before high levels of diastolic pressure mitigated the chance of the patient's remaining normotensive after operation. It was thought that nephrectomy in 1946 would have been preferable to ligation of aberrant vessels in view of the later developments. The production of ischæmic renal tissue as the result of vascular ligation might possibly be a prominent factor in the later development of a hypertensive state in certain cases. In any event, the present mild hypertension was preferable to the high and unstable pressures before nephrectomy, however late.

Dr. Duffy's third case was that of a man, aged 45 years, who was discovered to have a blood pressure reading of 210/130 millimetres of mercury on routine examination, in the absence of any past history of renal disease. There was no albuminuria or pyuria, and renal function tests gave normal results. An intravenous pyelographic examination revealed a hydronephrotic right kidney; the pyelogram from the left kidney was normal, and there was good dye excretion on both sides. Culture of ureteric specimens grew *Staphylococcus albus* from the right side, but there was no growth from the left. Right nephrectomy was performed by Mr. Kennedy Burnside, the patient's blood pressure falling to 115/80 millimetres of mercury in the post-operative period. Dr. Duffy said that over the nine months which had elapsed since the operation, the blood pressure recordings had been at normotensive levels around 130/90 millimetres of mercury. The hydronephrosis was due to a stricture at the pelvi-ureteric junction. That case, in which the duration of the hypertensive state prior to operation was unknown and the causal relationship of the hydronephrosis uncertain, was indicative of the need for thorough investigation of patients presenting with established hypertension of marked degree, and for preparedness to treat the unilateral renal disease surgically when it was found present.

Dr. Duffy then presented the case of a boy, aged 14 years, who had suffered a blow in the left loin when playing football a year earlier. The urine was blood-stained, and a pyelographic examination revealed a transverse rupture of the left kidney. He was treated conservatively, and his blood pressure rose from the admission level of 110 millimetres of mercury, systolic, to 175/95 millimetres of mercury on his discharge from hospital eight days later. Over the next three months his blood pressure readings remained at mildly hypertensive levels, around 150 to 160 millimetres of mercury, systolic, and 95 to 100 diastolic, before becoming stable, five months from the time of injury, at 120/80 millimetres of mercury.

Dr. Duffy discussed the case from the standpoint of the effect of injury to the kidney on the subsequent onset of hypertension.

Dr. Duffy's last case was that of a male, aged 50 years, who had presented in August, 1957, with a history of sudden severe pain in the left buttock when walking, which brought him to rest and then extended down the left leg. The pain went after he had rested for four or five days, after which time he experienced intermittent claudication in the left buttock and leg on walking uphill or 200 yards on the flat. On examination of the patient, the left femoral pulse was impalpable, but the popliteal, dorsalis pedis and posterior tibial pulsations could be just felt. The urine was free of albumin and cells, and the results of renal function tests and the pyelographic findings were normal. Aortography disclosed poor filling of the right common iliac artery, and no filling of the left common iliac artery. The left internal and external iliac arteries were filled by way of an anastomotic vessel arising mainly from the left fourth lumbar artery. The patient's blood pressure at the outset was recorded as 190/120 millimetres of mercury, but rose rapidly over the next month to 280/175 millimetres of mercury, from which level it was reduced by treatment with "Ansolysen" and "Serpina". However, it had been unstable, and diastolic pressures of 130 millimetres of mercury in both lying and standing positions had been common readings since then.

Dr. Duffy said that obstruction at the bifurcation of the aorta causing intermittent claudication in the buttock (Leriche syndrome) had been associated elsewhere with occlusion of one or other renal artery and severe hypertension, which had been relieved by nephrectomy on the affected side. The same association of common iliac and renal artery occlusion was possible in the case under discussion, and perhaps was responsible for the rapid production of high levels of systolic and diastolic blood pressure. That was possible despite the normal findings on intravenous pyelograms from either side, and further abdominal aortograms were required to demonstrate the impaired blood supply to one or other kidney.

Dr. Duffy finally said that he was using the case to demonstrate the importance of renal arterial disease in the production of hypertensive states. Renal ischæmia might result from a number of conditions including atheromatous thrombosis, embolism, aneurysms, constricting bands of fibrous tissue, thromboangiitis, etc., which might involve not only the main renal artery, but any of its branches or one of a number of anomalous renal arteries. Under those circumstances, Goldblatt's experimental lesion was reproduced in man, and the resultant hypertension should, if it was not of too long standing, respond to nephrectomy on the affected side.

The Assessment of Aortic Stenosis.

DR. JAMES M. GARDINER outlined the problems in the assessment of aortic stenosis. He said that they included the severity of the obstruction, the degree of associated aortic incompetence, the nature and severity of associated mitral valve disease, the severity of associated coronary artery disease and, in congenital cases, the site of stenosis.

Symptoms included syncope, angina pectoris, dyspnœa on effort, left ventricular failure and congestive cardiac failure. Those occurred relatively late in the natural history of the condition. Once left ventricular failure was present, the prognosis was limited, but the operative mortality rose. For patients with congestive failure the chances of a successful operation were small.

Dr. Gardiner then outlined the classical physical signs and discussed their variations. He drew attention to the aortic ejection sound, to the behaviour of the aortic element of the second heart sound, and to the atrial sound often present.

Discussing special investigations, Dr. Gardiner said that phonocardiography was useful in demonstrating the characteristic diamond-shaped ejection murmur, which might be differentiated from the pan-systolic murmur of mitral incompetence. The electrocardiogram was usually a fairly accurate guide to severity. Post-stenotic dilatation of the first part of the ascending aorta might be a feature on X-ray examination, which would also demonstrate calcification of the aortic valves. Intraarterial pulse tracings might be useful, but were occasionally misleading. In order to demonstrate the variation in systolic upstroke time of the pulse with differing stroke output, the Valsalva manœuvre had been used in a number of cases. Marked variation occurred in severe cases, but there was little variation when the obstruction was mild. The final special investigation used was left ventricular puncture. That test was performed in the operating theatre under basal sedation. The left ventricular pressure was obtained by passing a fine

needle via the cardiac apex into the cavity of the ventricle. When that was compared with the pressure in the brachial artery, the systolic gradient across the aortic valve was measured. That gradient gave a fairly accurate assessment of the severity of the lesion. It might be well over 100 millimetres of mercury in severe cases, and was less than 50 millimetres of mercury in mild cases. Under proper conditions the test had not proved to be disturbing to the patient. In certain congenital cases a catheter had been passed up into the aorta and a withdrawal tracing taken to localize the site of stenosis. Tracings in valvar and sub-valvar stenosis were shown.

Dr. Gardiner then showed patients to illustrate the points made. They included a man aged 65 years, suffering from severe aortic stenosis with syncopal attacks and right heart failure, whose condition was considered too advanced for operation. A second patient, a man aged 43 years, with aortic stenosis with slight incompetence, was about to undergo operation by an open approach. A man, aged 51 years, was suffering from aortic stenosis with significant incompetence; he was considered unsuitable for operation. A boy, aged 11 years, had congenital aortic stenosis of moderate severity. Two patients were shown after operation. They were a woman aged 46, who had had a successful operation for severe valvar stenosis, and a girl, aged 11, who had had an open operation for sub-valvar stenosis.

Parotid Tumours.

MR. ROBERT S. LAWSON showed a series of patients who had been treated surgically for parotid tumour. The histology of the tumours was illustrated by photomicrographs. The tumours were a mixed parotid tumour of varying cellularity and an adenolymphoma, and there was one case of Mikulicz's syndrome. Subtotal parotidectomy to the level of the facial nerve branches had been performed in cases in which adequate removal might otherwise endanger the facial nerve. In one case the actual tumour (adenolymphoma, as it proved) was found at operation to lie deep to the facial nerve branches. It was then possible to prise it out from the deep process of the gland without damage to the exposed nerve branches. The need for radical removal was illustrated by the case of a woman, aged 30 years, who had been first examined in 1954 with a twice-recurrent parotid tumour after local removal. The second recurrence then present (despite radon implants and X-ray therapy) was dealt with by parotidectomy; there had been no resultant facial weakness, and no further recurrence after nearly four years. In one young man there had been a small local recurrence in the operation scar two years later, evidently from an implant in the skin at the time of a biopsy performed prior to the original operation. Local removal had been followed by X-ray therapy with satisfactory result. Mr. Lawson said that it appeared that biopsy of a portion of the tumour should be avoided in favour of complete removal for identification. However, it was considered that local excision of small and early parotid tumours was adequate, and three patients were shown to illustrate the satisfactory long-term results of that procedure. In other words, not every minute parotid tumour required parotidectomy, but only tumours of large size and doubtful malignancy.

Radical Neck Dissection.

The second series of cases presented by Mr. Lawson comprised cases of epithelioma of the tonsil, tongue and lip (recurrent) and of adenocarcinoma of the thyroid, in each of which a radical neck dissection had been performed with satisfactory long-term results. In one case there had even been dissection of invaded glands for epithelioma of the tonsil, performed six years earlier, and the patient had been free from recurrence since operation.

Minor Rectal Conditions.

MR. GRAEME GROVE showed a number of patients to illustrate the post-operative treatment of minor rectal conditions including hæmorrhoids, fissure and fistula. There were several who had had primary skin grafting after excision of fistulæ.

Gastro-Enterological Problems.

MR. JAMES GUEST showed three patients to illustrate gastro-enterological problems.

The first patient was a woman suffering from ulcerative colitis, whose condition was slowly deteriorating. She was admitted to hospital for definitive medical treatment, but whilst she was undergoing it she suffered an arterial occlusion at the aortic bifurcation; surgery was considered too hazardous, and anticoagulants were contraindicated because of the bleeding from her bowel. The viability of her legs was in doubt for some time, and during that period severe and repeated hæmorrhages from the colon necessitated emergency colectomy and ileostomy, from which she recovered satisfactorily. Excision of the rectum was planned at a later date.

The second patient had complete prolapse of the rectum of nine months' duration; she had undergone multiple operations for fistula-in-ano 18 years previously, and since then had not been fully continent of fæces. The rectal prolapse had been repaired four months previously, the principles of the operation being complete mobilization of the rectum, repair of the pelvic diaphragm and reconstruction of the pelvic peritoneum so as to obliterate the deep recto-vesical pouch. Damage to the pubo-rectalis muscle following the previous fistula operation made the repair of the muscular pelvic diaphragm inadequate. It was considered that control of the rectal prolapse in that case was dependent on perirectal adhesions and exclusion of the recto-vesical pouch. Four months after operation the prolapse was adequately controlled. The case was regarded as a test case as to the relative importance of closure of the gap in the muscular pelvic diaphragm in the treatment of complete prolapse of the rectum.

The third patient was a male, aged 34 years, suffering from a pseudo-cyst of the pancreas. He had been treated by marsupialization, and the fistula had discharged for four to five months. Mr. Guest discussed problems of treatment of attacks of recurrent pancreatitis in that case and stressed the importance of alcohol as a precipitating factor.

Argentaffin Tumour of the Ileum.

MR. G. RUSSELL JONES showed a male patient, aged 70 years, who had presented on March 13, 1958, with the history of passing dark red blood per rectum for five days. Clinical examination of the patient revealed no abnormality, except some degree of obesity and a blood pressure of 220/110 millimetres of mercury. The hæmoglobin value was 65%. Sigmoidoscopic examination revealed no abnormality except for the passage of dark red blood from higher in the bowel. X-ray examination with a barium clysma (on two occasions) revealed a filling defect in the region of the ileo-caecal valve. The appendix was long, and filled well. No ileal reflux was observed at any time during the examination. Laparotomy on March 23 revealed a mobile tumour the size of a walnut in the caecum. The liver was normal. A right hemicolectomy was performed. Examination of the operation specimen revealed a pedunculated argentaffinoma of the terminal portion of the ileum which had intussuscepted through the ileo-caecal valve. Metastases were present in the regional lymph glands.

Mr. Russell Jones said that the patient was shown because of the unusual mode of presentation of the tumour—melæna. Argentaffin tumours rarely ulcerated deeply enough to cause gross bleeding. It was interesting to note that that patient had denied any colicky pain or bowel disturbance, such as might have been expected to follow the intussusception. There was no history of cyanotic attacks, and the hypertension was regarded as essential in origin and not related to excess serotonin production by the tumour.

Penetrating Wound of Abdomen by Large Post.

MR. J. K. FRANCIS presented a patient who had survived gross abdominal trauma. The patient, a man aged 35 years, had been involved in a motor-car accident, in which a post measuring three inches by four inches and some six feet in length had smashed through the radiator of his car, impaled him through the right side of his abdomen and finally pinned him to the seat of the car by passing through the said seat. His local doctor had given him an injection of morphine, and with great courage on the part of all concerned had sawn off the two protruding ends of the post.

On the patient's admission to hospital, some 18 inches of the post was still piercing his right flank. An immediate laparotomy was performed with concomitant resuscitation. A transverse incision was made in the right flank to join the extruding ends of the post. The wound was grossly soiled and there was a considerable defect of the entire abdominal wall, anteriorly and posteriorly. Inside the abdomen the post had passed between the ascending colon laterally and the vena cava and right ureter medially. There were several perforations of the transverse and ascending colon, together with a perforation of the terminal portion of the ileum. The right kidney, ureter and vena cava were somehow intact. The post was gingerly removed, and a right hemicolectomy was performed with end-to-end anastomosis. Closure of the peritoneum was barely possible, but adequate *débridement* of the wound was impossible owing to the patient's general condition.

He had a stormy convalescence, developing severe cellulitis of the abdominal wound together with a fæcal fistula.

At subsequent operations, multiple subphrenic abscesses were drained; a terminal ileostomy was established and the distal end of the colon was closed and returned to the abdomen. At that stage there was a good three-fingers' breadth of liver completely exposed in the wound. That could only be covered with *tulle gras* and repeated dressings.

The patient then slowly improved until a further operation was performed and an ileo-transverse colostomy established. At that stage the liver was covered by clean granulation tissue. At a later date, coverage by split-skin grafting was performed. At the time of the meeting the patient had a diffuse bulge of his abdominal wall in that area, controlled by a corset.

Mr. Francis said that during all the procedures the patient had lost considerable weight and condition, but since his discharge from hospital (some four months after his admission) he had thrived magnificently. Initially he had had severe episodes of diarrhœa, but they had now almost completely subsided. The fortitude of the patient with such a gross injury and with successive complications and operations, had been truly astounding.

Gall-Stone Ileus.

Mr. Francis then showed two patients with gall-stone ileus, and discussed certain features of the diagnosis and treatment of such patients.

The first patient was a woman, aged 79 years, with a history of intermittent colicky abdominal pain, vomiting, constipation and abdominal distension of six days' duration. Her only relevant past history was some long-standing flatulent dyspepsia. She had had no previous abdominal operation. The vomiting was fæculent in nature when the patient was examined. On examination, she was a dehydrated, elderly woman with a normal temperature. The abdomen was markedly distended and small bowel patterns were visible. Rectal examination revealed no abnormality. X-ray examination of the abdomen revealed multiple distended loops of small bowel containing fluid levels, but no distension of the caecum or large bowel was detected. The appearance was suggestive of small-bowel obstruction. Serum electrolyte studies showed lowered levels of sodium, chloride and potassium, with an elevated bicarbonate level. A hæmatocrit reading showed hæmoconcentration, and the blood urea level was 75 milligrammes per 100 millilitres. The pre-operative diagnosis of gall-stone ileus was made, in view of the long duration of symptoms in an elderly female with a "virgin" abdomen, the intermittent nature of the symptoms and the presence of fæculent vomiting.

Pre-operative gastric suction, the intravenous administration of fluid and electrolyte replacement were undertaken, and at laparotomy a large, non-facetted gall-stone was found in the terminal portion of the ileum, causing obstruction at that level. The gall-stone was removed. The distended small bowel was aspirated, and no further stones were felt; the gall-bladder area was palpated, but was bound down with fibrotic adhesions. Her convalescence was uneventful, apart from mild wound infection.

The second case of gall-stone ileus presented by Mr. Francis had many similar features. The patient was an elderly woman, aged 66 years, with a five days' history of intestinal colic, abdominal distension and constipation, following an initial bout of diarrhœa. She had been vomiting profusely for some hours prior to her admission to hospital. The only relevant event in her past history was an attack of pain over the right costal margin some eighteen months previously. On examination, the patient was somewhat dehydrated and her temperature was subnormal. Abdominal examination revealed no scars or herniæ, with only slight distension. There was some tenderness under the right costal margin and in the left iliac fossa. On rectal examination a mobile mass some one and a half inches in diameter was palpable in the pelvis. X-ray examination of the abdomen revealed a few coils of distended small bowel containing mainly fluid and a little air and showing fluid levels. Only a minimal amount of gas and no fæcal material was seen in the large bowel. The findings were highly suggestive of mechanical obstruction of the small bowel towards its distal end. Serum electrolyte studies showed slightly lowered levels of sodium and chloride, but normal potassium, bicarbonate and hæmatocrit figures.

The patient was observed for some hours before operation while resuscitation with fluid given intravenously and gastric aspiration were undertaken. A further X-ray film of the abdomen revealed the same findings as previously and operation was performed. At laparotomy a large gall-stone was found obstructing the terminal portion of the ileum. The gall-stone was removed and found to be non-facetted; the distended small bowel was aspirated, and no further gall-stones were to be felt in the alimentary canal. The gall-bladder was small and fibrotic and adherent to the duodenum. Convalescence was uneventful, apart from a mild wound infection.

Mr. Francis then mentioned some of the problems in diagnosing gall-stone ileus, and enumerated the suggestive features. (i) The patient was often an elderly female with non-strangulated small intestinal obstruction, and the diagnosis was particularly likely if there were no abdominal scars or herniæ present. Vick had shown that at least 25% of those patients over the age of 70 years have a gall-stone obstructing the bowel. (ii) The intermittency and long duration of the obstructive symptoms (due to the stone's passing along the bowel) was most suggestive. (iii) Profuse or fæculent vomiting was present on admission to hospital in a high percentage of such cases. (iv) A past history of biliary symptoms might be elicited, but was usually absent. Mr. Francis said that the symptoms were the main feature in diagnosis, as the signs were usually few. The patient was generally dehydrated and had considerable electrolyte depletion. Abdominal distension might be minimal, as there was no "closed loop" in the obstruction; the distension was also often masked by obesity. X-ray examination might be of help: (i) it might reveal signs of small-bowel obstruction—distension and fluid levels; (ii) occasionally a radio-opaque gall-stone might be visualized, often only in an oblique or lateral film; (iii) air might occasionally be present in the biliary passages.

Mr. Francis then stressed the high mortality in most cases of gall-stone ileus, and said that it was due to the lateness of diagnosis and the advanced age of the patient. Prior to 1940 the mortality rate was 50% to 60%. Since 1940 it had fallen to 33% in published series, compared with a mortality rate of less than 10% from other causes of simple bowel obstruction.

Discussing the treatment of the condition, Mr. Francis said that it involved, first of all, pre-operative restoration of fluid and electrolyte balance by intravenous replacement therapy, together with alimentary aspiration. Secondly, laparotomy was required. Points to be stressed in operating were: (i) Aseptic removal of the gall-stone by a longitudinal incision repaired transversely. The stone is usually impacted and pushing it in a retrograde direction was generally impossible. (ii) Deflation of the distended small bowel above the level of obstruction. (iii) Inspection of the gall-stone for facets. If they were noted, then a further stone might be present. The rest of the intestine was palpated to avoid a recurrence of obstruction due to a missed stone. If obstruction did recur, it was usually during convalescence, and diagnosis was extremely difficult. (iv) Palpation of the gall-bladder area. The gall-bladder was usually fibrotic and shrunken. If a large stone was palpable and the patient's condition satisfactory, that stone should be removed by cholecystostomy, otherwise the gall-bladder area was left severely alone. After operation, wound infection and slow healing were common.

Repair of Cardiac Defects.

MR. K. N. MORRIS showed a series of patients to illustrate various aspects of the repair of cardiac defects by open techniques. He also demonstrated the pump oxygenator used during the operations.

Ventricular Septal Defect.

The first patient shown was a boy, aged three and a half years, who had suffered from pneumonia at the age of three months. When he was examined at that time he had the signs of a large ventricular septal defect, with a large heart, chest deformity, and dyspnœa. He settled down fairly well, with an occasional chest infection, until the age of three years, when, after a severe attack of bronchitis, he was found to have signs of mild cardiac failure, quickly responding to treatment. However, he was becoming more easily tired.

On examination he was acyanotic. The radial pulse was small and the femoral pulses were normal. There was a left ventricular cardiac impulse. A loud systolic murmur and thrill at the lower left sternal edge was present. A mid-diastolic murmur was heard at the apex. The second heart sound was split in the pulmonary area, with a moderate pulmonary element. A phonocardiographic examination revealed a loud pan-systolic murmur at the left sternal edge, maximal in the fifth intercostal space. At the apex there was a third sound with a mid-diastolic murmur. The second heart sound was constantly split to 0·04 second, the pulmonary element being louder than the aortic in the pulmonary area. An electrocardiographic examination revealed left and right ventricular hypertrophy. X-ray examination of the chest revealed considerable cardiac enlargement, with pulmonary œdema. Cardiac catheterization revealed a large left-right shunt into the right ventricle; the pulmonary blood flow was four times the systemic. The pulmonary arterial pressure was 71/41 millimetres of

mercury when the femoral arterial pressure was 102/69. There was no systolic pressure gradient within the right ventricle. The arterial oxygen saturation was normal. Pulmonary vascular resistance was 15% of the systemic.

At operation on July 23, 1957, repair of the ventricular septal defect was undertaken with the use of a pump oxygenator. The defect was about 1·5 centimetres in diameter. There was no atrial defect. There was a left superior vena cava. His progress was very satisfactory. At the time of the meeting he had only a faint systolic murmur and no mid-diastolic murmur. His heart size appeared to have decreased.

Mr. Morris next showed a girl, aged nearly six years, who had failed to thrive as an infant and had been in hospital for many months. She was examined at the age of six months and the diagnosis of ventricular septal defect was made. She had gradually picked up and had been reasonably well in latter years. She was small and considerably underweight (29 pounds), but fairly active at school.

On examination she was undersized but acyanotic; a chest deformity was present. The radial pulses were small and the femoral pulses were present. There was a left ventricular cardiac impulse. There was a moderate systolic murmur, with a faint thrill, at the lower left sternal edge; a somewhat shorter systolic murmur was heard in the pulmonary area. A mid-diastolic murmur was heard at the apex. The second heart sound in the pulmonary area was loud and not clearly split. A phonocardiographic examination revealed a moderate early systolic murmur, which faded away before the second heart sound was recorded at the left sternal edge and pulmonary area. At the apex there was a loud mid-diastolic murmur. At the pulmonary area there was an ejection sound. The second heart sound was very loud and "broad", but not clearly split even on inspiration. An electrocardiographic examination revealed right and left ventricular hypertrophy. An X-ray examination of the chest revealed considerable cardiac enlargement, with a large pulmonary trunk and well marked pulmonary plethora. Cardiac catheterization on August 22, 1957, revealed a moderate left-right shunt into the right ventricle. The pulmonary flow was twice the systemic. The pulmonary artery pressure was 76/48 millimetres of mercury when the femoral arterial pressure was 94/56. The arterial oxygen saturation was 91%. The pulmonary vascular resistance was 40% of the systemic.

At operation on April 15, 1958, closure of the ventricular sepal defect was undertaken with the use of the pump oxygenator. In view of the marked pulmonary hypertension, the ventricular septal defect was closed via the right atrium and tricuspid orifice, which gave quite good access to the ventricular septal defect. That meant that the child had an uninjured right ventricle with which to face her convalescence. Mr. Morris said he thought that that was of importance in enabling the sick child to be operated upon successfully.

Infundibular Pulmonary Stenosis.

Mr. Morris finally showed a boy, aged ten and a half years, whose heart murmur had been discovered early. He had had very little, if any, real limitation of activity, although he was subject to bronchitis when younger. His colour had always been normal.

On examination the boy was acyanotic and his pulses were normal. There was a rather prominent "a" wave in the jugular venous pressure. No left ventricular impulse was present. There was a very loud systolic murmur, with a thrill, maximal in the third left intercostal space. The second heart sound was single. An occasional third sound was heard at the apex. A phonocardiographic examination revealed a loud pan-systolic but diamond-shaped murmur, which was recorded maximally at the third left intercostal space, poorly in the aortic area. The second heart sound was soft, and no separate pulmonary element could be detected. An electrocardiographic examination revealed right axis deviation, but no other abnormality. An X-ray examination of the chest revealed slight to moderate cardiac enlargement. There was some fullness below the pulmonary artery segment. The pulmonary vascular markings were normal or possibly slightly increased. At cardiac catheterization on December 23, 1955, the pulmonary artery pressure was found to be 18/8 millimetres of mercury. On withdrawal of the catheter into the right ventricle, there was a fall of diastolic pressure to 18/2 millimetres of mercury, with a sharp rise of systolic pressure about three centimetres below valve level to 106/2 millimetres of mercury. There was no definite evidence of a left-right shunt. Under "Pentothal" anæsthesia, the right ventricular pressure fell to 53/0 millimetres of mercury, when the femoral arterial pressure was 90/47 millimetres of mercury and the arterial oxygen saturation was 90%.

At operation on February 25, 1958, resection of the area of infundibular stenosis was undertaken with the use of the pump oxygenator. The child had an uninterrupted convalescence and was gaining weight and strength rapidly.

Cancer of the Breast.

MR. D. B. PEARCE and DR. E. A. FARRAN showed patients illustrating the management of cancer of the breast. It was pointed out that 60% of new patients with cancer of the breast had the disease limited clinically to the breast tissue and axillary glands, and for that group radical surgery was indicated. Post-operative deep X-ray therapy had been shown to reduce considerably the risk of recurrence and to give a significant improvement in the percentage of five-year survivals. Patients with breast cancer extending beyond the breast tissue and axillary glands usually required a combination of various measures to control the growth. The control of an extensive cancer of the breast by deep X-ray therapy was demonstrated, and X-ray films illustrated the use of deep X-ray therapy in the control of secondary deposits in bones.

It was stated that the hormonal treatment of breast cancer included surgical or radiological induction of the menopause, surgical removal of the adrenal glands or the pituitary, and the medical use of testosterone, œstrogens and cortisone. Chemotherapy with "Nitromin" had a small but useful place in some advanced cases.

SISTER HEWITT, of Berlei, Limited, demonstrated the improvement in appearance and in the comfort and confidence of the patient with the modern "identical breast form" after radical mastectomy.

Plastic Repair Around Head and Neck.

MR. J. A. SNELL showed a series of patients to illustrate methods of plastic repair around the head and neck. In most cases repair followed excision of epitheliomata and basal cell carcinomata. Various types of free grafts and flaps were demonstrated.

The last patient was a woman, aged 70 years, who had been completely scalped when her hair became caught in machinery. The entire scalp, including the eyebrows and the skin from the back of the neck to the level of the second thoracic vertebra, was avulsed. Repair was obtained by immediate application of sheets of split skin graft. Two weeks after the accident, healing was almost complete.

Undescended Testes.

MR. E. DURHAM SMITH reviewed the short-term operative results of 22 undescended testes in 17 boys under 14 years of age treated over the last year. Ten boys had unilateral undescended testes (right four, left six) and in seven the condition was bilateral. Fifteen of the testes had been classified as ectopic, all being in the superficial inguinal pouch. The operative results of orchidopexy were classed as good in 13 cases, as indicated by a normal-sized testis lying at the bottom of the scrotum, and poor in two cases, in that both the testes were smaller than normal and lying only as far as the neck of the scrotum. Of a further five cases, classified as "arrested in the line of normal descent", good results were obtained in three and poor in two; both of the last-mentioned patients had small, poorly developed testes for which orchidectomy was performed. In a further two cases no testis was found on the explored side; in one the condition was secondary to an orchidopexy eight years earlier, and in the other a vas and spermatic cord structures were present, but no testis.

Mr. Durham Smith said that the results indicated the favourable prognosis in ectopic testes when the cord was long, compared with those arrested in the line of normal descent; boys with the latter condition were more likely to have short cords and poorly developed testes.

A number of boys were shown to illustrate (*a*) the clinical types of undescended testes and (*b*) the operative results.

Mr. Durham Smith said that no child had received treatment by hormones, as it was thought that the only possible indication for hormone treatment was bilateral cryptorchidism with proven evidence of other endocrine dysfunction. Although there were two "fat boys" with somewhat hypogonadal features, their endocrine lack could not be demonstrated chemically and there seemed no rationale for hormone therapy.

In the decision whether operation should or should not be performed, three questions must be answered. The first was in which circumstances one should await spontaneous descent. The policy adopted had been to wait if the testes were "retractile" and if a unilateral undescended testis was riding high at the neck of the scrotum. The second question

related to the use of hormones; Mr. Durham Smith said that he had already dealt with that. The third question was which testes should be operated on, and when. The evidence for the answers was reviewed, including the risks of not operating, and it was stated that the policy had been to operate on all patients with undescended testes, preferably between the ages of six and nine years, who did not fit into the first or second category.

Mr. Durham Smith finally said that the operative procedure adopted and the reasons for operation would vary in different cases. In unilateral cases, if the testis was of normal size, orchidopexy was the aim, and was easy in ectopic testes; but it sometimes required multiple stages when the testes were arrested in the line of normal descent. If the testis was small, however, it did not often develop even if placed in the scrotum; unless the testis was only slightly smaller than normal, orchidectomy was preferred to orchidopexy. Very few patients with unilateral undescended testes and short cords might be suitable for division of the testicular vessels in order to achieve orchidopexy. In bilateral undescended testes the thesis was developed that both sides should be explored at once before the definite operative step was taken on one or other side. For example, when only one testis was found, it should be replaced in the abdomen—probably the only indication for abdominal replacement—in order to take no chances of losing androgen function. It was stressed that when two testes were discovered an attempt to achieve orchidopexy, even with multiple stages, should be made on one side and the result finalized before an attempt was made on the second side. Only then could the correct decision be made as to the operative procedure on the second side. For example, if the first side succeeded, an orchidopexy or orchidectomy might be performed on the second side, depending on the development of that testis; if the first side failed and the testis became atrophic, whatever the second testis was like it should be preserved, and probably was best replaced in the abdomen.

FEDERAL COUNCIL.

The following correspondence is published for the information and interest of members of the British Medical Association. It relates to the conveying of congratulations on behalf of the Association in Australia to the General Medical Council on its Centenary year.

[COPY.]

FEDERAL COUNCIL OF THE BRITISH MEDICAL ASSOCIATION IN AUSTRALIA.

16th December, 1958.

W. K. Pyke-Lees, Esq.,
Registrar,
General Medical Council,
44 Hallam Street,
London, W.1, England.

Sir,

In the Centenary year of the General Medical Council the British Medical Association in Australia desires to offer its congratulations to the Council. It joins with other British Commonwealth bodies in honouring the Council's achievement especially in maintaining the highest standards both of professional competence and of medical education.

It seems appropriate that the Council, created when those it was to govern still called themselves apothecaries, should have been given the duty, so well fulfilled, of compiling and publishing an official British Pharmacopœia.

The standards of regulation and discipline set by the General Medical Council have been adopted by the licensing bodies in Australia, where, too, its prescribed standards of professional education and skill are zealously maintained.

Faithfully yours,
(Sgd.) J. G. HUNTER,
General Secretary.

GENERAL MEDICAL COUNCIL.

44 Hallam Street,
London, W.1,
2nd February, 1959.

Dear Sir,

I have shown to the President of the Council your letter of December 16, conveying on behalf of the British Medical Association in Australia congratulations on the Centenary of the General Medical Council, and I am desired by the President to express his warmest appreciation and thanks for the terms of your letter. The Council has always attached the greatest importance to its relations with Commonwealth countries, and the long history of reciprocity with the various States in Australia has been a matter of much satisfaction to past and present members of the Council. As the President mentioned at the Special Centenary Session of the Council, medical qualifications granted in Victoria, New South Wales and South Australia were recognized by the Council as far back as the period between 1890 and 1893. Queensland qualifications followed in 1942, and now that the Privy Council has agreed to extend Part III of the Medical Act, 1956, to Western Australia the Council looks forward to the day when medical qualifications granted in that State will in due course become registrable in our Commonwealth List.

Yours faithfully,
(Sgd.) WALTER PYKE-LEES.

The General Secretary,
Federal Council of the British Medical Association in Australia,
135 Macquarie Street,
Sydney, New South Wales.

Correspondence.

THE PATIENT, THE SURGEON AND THE ANÆSTHETIST.

SIR: In your issue of January 3, 1959, Dr. M. P. Susman poses a question which is directed specifically to anæsthetists.

This question is one which has been discussed a number of times by the anæsthetists in this hospital, primarily because we have from time to time patients presented to us who fall into the category included in the question. Our reply to this question would be along the following lines: "Yes, we will anæsthetize your patient and will do our best to maintain or improve his condition during the operation. Of course, you realize, as well as we do, that the patient may not survive his time in the operating room."

One cannot see that there is any other choice open under the circumstances posed in the question. If, in the mature judgement of the surgeon, who has probably called other people, including the anæsthetist, into consultation, the patient will succumb if nothing is done, then certainly one must give him a chance, no matter how slim that may be. As one with years gains a certain amount of experience in medicine, one is forced to the conclusion that never can one act with the authority of a Deity. If a chance exists, no matter how slim it may be, that chance must be offered to the patient.

Yours, etc.,
C. R. STEPHEN, M.D.,
Professor of Anesthesiology.

Duke Hospital,
Durham,
North Carolina,
U.S.A.
February 9, 1959.

THE FUTURE OF THE AUSTRALIAN ABORIGINAL.

SIR: There is a desire these days to assimilate the Australian aboriginal into the national life. Most writers on the subject do not seem to realize that the aborigines and the mixed bloods, which are practically the only coloured people in New South Wales, present quite different problems.

When the problem of the mixed bloods is being considered, it is the problem of the poor white more than that of the primitive aboriginal native. They need education and discipline before they are fit to play their part in the national life. The children follow the bad examples of their parents, and these unhappy people are ever increasing. I have recently encountered four coloured girls with 28 children between them, and not one father to support any of them. I do not think that many of them worry about citizenship, except it means that they can buy beer at a bar counter instead of getting liquor by devious paths.

These people should be sheltered and trained in decent reserves, and sent out to work or settled in the community when they are fit to do so. The reserves in New South Wales are too many and far too small. They should be big enough to train the men in stock work, shearing, carpentering and so on. The settlements on the fringes of towns should be abolished, and all those who cannot find work or accommodation sent to reserves temporarily. Also those who have numerous convictions for drunkenness should be committed to reserves with their families. Short-term gaol sentences are worse than useless. To reserves also should be sent these unfortunate girls with their pathetic little children. Here in Armidale we have one man with 12 children who has had 47 convictions for drunkenness in two years.

These people cannot learn a better way of life if they are not taught. You might just as well expect a child to pass the intermediate examination without going to school. The problem is far more one for the social and medical worker than for the anthropologist.

I have worked amongst these people for years. Only yesterday did a sister and myself chase the little darkies around the rubbish dumps and pull them off old cars and from under blackberry bushes to immunize them against diphtheria.

Yours, etc.,
ELLEN M. KENT HUGHES.

141 Faulkner Street,
Armidale,
N.S.W.
February 9, 1959.

Post-Graduate Work.

SURGICAL SEMINARS AT THE ROYAL NORTH SHORE HOSPITAL OF SYDNEY.

THE following is the programme of surgical seminars to be held at the Royal North Shore Hospital of Sydney from March to June, 1959.

March 9: "Obstructive Jaundice", Dr. E. Finckh, Dr. D. W. Piper, Mr. E. Langley.

April 13: "Cancer of the Colon", Mr. V. E. Barling, Mr. V. H. Cumberland.

May 11: "Abdominal Pain in Children", Mr. N. A. Fowler, Mr. F. N. Street.

June 8: "Cancer of the Stomach", Dr. Stanley Goulston, Mr. E. H. Goulston.

The seminars will be held on the second Monday of each month at 4.15 p.m. in the Students' Lecture Room. All members of the medical profession are invited to attend.

The Royal Australasian College of Physicians.

VICTORIAN STATE COMMITTEE.

THE Victorian State Committee of The Royal Australasian College of Physicians has arranged for Dr. A. E. Doyle, of the Department of Medicine, University of Melbourne, to deliver a lecture entitled "The Adrenal Cortex and Hypertension" in the lecture theatre of the Royal Australasian College of Surgeons, Spring Street, Melbourne, on Tuesday, March 17, 1959, at 5.15 p.m. All members of the medical profession are invited to be present.

Notes and News.

World Medical Association.

The following items of news have been received from the World Medical Association.

The Philippines Medical Association, with the help of 15 medical and allied organizations, has designated the period

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JANUARY 24, 1959.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	2	2(2)	4(2)	..	..	..	..	..	8
Amœbiasis	..	..	..	..	..	..	1	..	1
Ancylostomiasis	..	..	..	..	..	..	3	..	3
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	1	..	..	..	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	1(1)	..	..	..	..	..	..	1
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	3(1)	11(8)	4(4)	..	3(2)	..	..	1	22
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	..	4(4)	1(1)	3(1)	..	8	..	16
Encephalitis	1	2(2)	..	..	..	..	..	..	3
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	59(16)	12(8)	9(4)	5(4)	1	1	2	..	89
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	1	..	..	..	1
Leptospirosis	..	..	..	..	..	..	..	..	..
Malaria	..	..	1(1)	..	..	..	..	..	1
Meningococcal Infection	..	..	..	..	1	..	..	..	1
Ophthalmia	..	..	..	..	2	..	..	..	2
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	1(1)	..	..	..	..	..	..	..	1
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	1(1)	1(1)	1	..	..	..	..	..	3
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	15(12)	1(1)	14(2)	24(23)	3	1	1	59
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	5(5)	5(2)	1(1)	..	..	..	..	..	11
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1(1)	..	..	..	..	..	1
Trachoma	..	..	..	..	1	..	21	..	22
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	20(10)	12(10)	19(6)	6(2)	8(6)	4(1)	..	3	72
Typhoid Fever	..	..	..	1(1)	..	..	..	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

May 7 to 10, 1959, "Health Week". The programme is designed to focus medical and public attention on the value of health and the importance of providing a scientifically sound medical programme in order to raise the standards of public health care.

The fifteenth general assembly of the Japan Medical Congress will be held in Tokyo from April 1 to 5, 1959. The scientific session is under the joint auspices of the Confederation of the Medical Societies of Asia and Oceania and the Japan Medical Congress.

The Brazilian Medical Association has postponed its second congress, originally to take place in the first week of September, until September 26 to October 4, 1959. The theme of the congress is "Improving Medical Care Standards".

Rheumatology: Acqui Terme Prize.

The Italian thermal city of Acqui Terme, under the auspices of the Società italiana di Reumatologia, is offering the fourth international prize in rheumatology, the sum of 1,500,000 Italian lire. The closing date is May 31, 1959. Competitors are asked to submit in Italian or French a brief résumé of the work to be presented. The names of the members of the international panel of judges will be made public after May 31. All information may be obtained by writing to the following address: Azienda Autonoma di Cura di Acqui Terme, Piemonte, Italia.

North Queensland Medical Conference.

The next bi-annual North Queensland Medical Conference will be held in Rockhampton for one week from July 24 to 30, 1960. The plenary session of the conference is to be on "Traffic Injuries", and the remainder of the time will be directed to discussion of subjects of interest to general practitioners. All inquiries in connexion with the conference should be addressed to the Secretary, Dr. J. H. Learmonth, Commercial Building, William Street, Rockhampton, Queensland.

Riker Laboratories (Aust.) Pty. Ltd.

We have been advised that the Riker Laboratories (Aust.) Pty. Ltd. advertisements for "Myophane" which appeared on the art paper pages xvii and xviii in last week's issue did not include the company's Australian address. This is 62 Alexander Street, Crows Nest, N.S.W.

First National Medical Congress of the Spanish Red Cross.

The first National Medical Congress of the Spanish Red Cross will be held in Madrid from May 20 to 23, 1959, under the presidency of Dr. D. Carlos Blanco Soler. The programme will cover the following subjects: radioactivity, congenital heart disease, rehabilitation, transfusion. There will also be a symposium on emergency medicine and surgery, presided over by Dr. Blanco Soler.

Further information, programmes and membership application forms may be obtained from the Secretariat of the Congress, Paseo de Eduardo Dato, 16, Madrid.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Aroney, Charles James, M.B., B.S., 1957 (Univ. Sydney), 70 Railway Parade, Cabramatta.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association (qualifications being M.B., B.S., 1959 (Univ. Sydney) (provisional registration) unless otherwise stated): Antonenko, Nikolai; Biddulph, Robert Arthur John; Garlick, David George; Gluskie, Clarence Alexander; Goulston, Kerry John; Houghton, Graeme Warwick; Kahans, Daniel; Morris, Peter Leo; Poole, Alan Gregory; Raik, Eva; Re, Bartolo John; Ronai, Ann Kathleen; Troup, Ann; McDonald, Robert Concord; Cockburn, Campbell Geoffrey, M.B., B.S., 1957 (Univ. Sydney); Coorey, Glen John, M.B., B.S., 1957 (Univ. Sydney); Siddall, David James, M.B., B.S., 1956 (Univ. Sydney).

Deaths.

THE following death has been announced:

SMITH.—Graham Beresford Smith, on February 13, 1959, at New Lambton, New South Wales.

Diary for the Month.

MARCH 3.—New South Wales Branch, B.M.A.: Organization and Science Committee.
MARCH 4.—Western Australian Branch, B.M.A.: Branch Council.
MARCH 5.—New South Wales Branch, B.M.A.: Public Relations Committee.
MARCH 5.—South Australian Branch, B.M.A.: Council Meeting.
MARCH 6.—Queensland Branch, B.M.A.: General Meeting.
MARCH 7.—Tasmanian Branch, B.M.A.: Annual Meeting.
MARCH 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee; Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales. Anti-Tuberculosis Association of New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given, surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £5 *per annum* within Australia and the British Commonwealth of Nations, and £6 10s. *per annum* within America and foreign countries, payable in advance.